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THERAPEUTIC CASTRATION FOR ADVANCED MAMMARY CANCER

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AN appreciation of the relationship of mammary cancer to the endocrine glands has evolved during the last century from a variety of observations in the clinic and laboratory. As long ago as 1836 Sir Astley Cooper[6] observed patients suffering from advanced cancer of the breast and concluded that the tumor grew rapidly prior to menstruation and that the rate of growth decreased after the menstrual period. Sixty years later Sir George Beatson[2] reported for the first time that widespread mammary cancer regressed for a period of time after bilateral oophorectomy. Subsequently, the reports of Lett,[13] Torek,[18] Lambot,[11] and Boyd[5] confirmed Beatson's observations. In 1922 de Courmelles[7] demonstrated that irradiation of the primary tumor and of both ovaries was of value in treating cancer of the breast. Modern endocrine therapy of mammary cancer, however, began in 1951 when Huggins[10] proved that certain cancers of the breast would undergo regression following removal of the ovaries and the adrenal glands. He postulated that tumor regression was obtained by the elimination of the patient's estrogen production.

Sixty-three patients with advanced mammary cancer were treated at the University of Michigan Medical Center by operative or irradiation castration. All 63 patients in our series were females. Two patients could not be traced after they left the hospital and 1 patient died in the immediate postoperative period. Sixty females, then, constitute the basis of this report. They have been followed to the time of death or to the time of this writing.

The tumors of all patients were so advanced that resection, local irradiation, or irradiation of a single metastatic focus was impractical. Operative castration was performed on 46 patients, irradiation on 14. The latter method of castration was accomplished by high voltage radiation of the pelvis, the dose of which in the ovary varied from a minimum of 625 r to about 1,100 r in 10 days or less.

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The patients in this series had received no significant therapy for at least 6 weeks prior to castration with the exception of 2 patients in whom distant symptomatic sites were irradiated simultaneously with castration. In these patients other areas of involvement by tumor were present for our observation in determining the effect of castration. In all patients a microscopic diagnosis of mammary cancer was made.

A variety of metastases to skin, subcutaneous tissue, lymph nodes, bone, and lung comprised the measurable evidence of our patients' disease. The response to castration was judged clinically. Objective remissions were recorded when the patient showed evidence of regression of lesions for at least 60 days without progression at any site. In a few patients in whom we were unable to evaluate the tumor objectively, but in whom there was overwhelming evidence of remission such as return of motor functions, absence of pain, or a great increase in well-being, a subjective remission was recorded. Laboratory determinations such as hemoglobin concentration, erythrocyte count, and others were not used to evaluate the response to castration.

Castration failed where the cancer either did not regress or actually enlarged. Remissions were considered terminated with the addition of any other mode of therapy or with evidence of progression of the disease at any site.

In all patients, the age of the patient, duration of the disease, length of remission, and length of life following castration were determined. The sites of neoplastic involvement and the microscopic morphology of the tumor were noted.

SELECTION OF PATIENTS FOR CASTRATION

In our clinic, hormonal additive or ablative therapy is withheld until local resection or local irradiation is no longer feasible and the patient shows obvious progressive disease. We have generally not employed additive therapy early in the course of the disease as we have not been able to find a satisfactory principle for choosing one steroid over another. Also, the administration of steroids is potentially dangerous because of their side effects and the possibility of tumor activation. We generally prefer ablative therapy because the remission rate with the various ablative procedures is higher than with additive therapy.

The patients in our series were not selected at random. In general they were patients in whom we believed there was ovarian activity, and whose tumor may have given some indication of being hormonally sensitive.

In choosing candidates for therapeutic castration, we have usually limited ourselves to patients who were premenopausal, a few years past the menopause, or far past the menopause with evidence of significant estrogen production.

RESULTS

All patients who experienced objective remissions also obtained subjective remissions. Frequently the subjective remissions persisted for some months after the objective remission was considered terminated. Of the 60 patients, 24 (40 per cent) experienced remissions (24 subjective, 21 objective) (Table I). In 36 cases (60 per cent) the treatment was considered to have failed.

Forty-six patients were castrated by oophorectomy. Sixteen (34.7 per cent) experienced subjective remissions while only 13 (28.4 per cent) obtained objective remissions. Castration by operation in 30 patients (65.2 per cent) failed.

Fourteen patients underwent irradiation castration. Of this group, 8 (57.1 per cent) experienced subjective remissions while only 7 (50 per cent) achieved objective remissions. Six (42.9 per cent) of the 14 failed to improve.

Age.—The average age of the patients benefiting from castration was 42.2 years with a range of from 31 to 61.5 years. The "failure" group was older. Here the average age was 47.3 years with a range of from 32.2 to 68.0 years. There is no significance in the difference in ages of the 2 groups; rather, the relative youth of the "successful" group is probably a reflection of the larger number of premenopausal patients included—33, as opposed to 27 postmenopausal patients.

TABLE I. RESULTS OF THERAPEUTIC CASTRATION

	OBJECTIVE REMISSION		SUBJECTIVE REMISSION		FAILURE	
	NO.	%	NO.	%	NO.	%
Entire group						
60	21	35	24	40	36	60
46 operative	13	28.4	16	34.7	30	65.2
14 irradiation	7	50	8	57.1	6	42.9
Premenopausal group						
33	14	42.4	17	51.5	16	48.5
26 operative	9	34.6	11	42.3	15	57.7
7 irradiation	5		6		2	
Postmenopausal group						
27	6	22.2	7	25.8	20	74.1
20 operative	4		5		15	75.0
7 irradiation	2		2		5	
"Truly" postmenopausal group						
19	5	26.2	5	26.2	14	73.7
17 operative						
2 irradiation						

Duration of Disease.—Duration of disease was designated as the time from the first sign or symptom of the mammary cancer to the time of castration. The patients who obtained remissions had an average duration of disease of 82.0 months with a median of 31 months and a range from 3 to 136 months. The patients failing to respond to castration had an average duration of 27.7 months, a median of 17 months, and a range of from 1 to 132 months. There is no correlation between age of the patient and duration of the disease.

Duration of Remission and Length of Life.—In the group benefiting from castration the average duration of life after castration was 13.9 months, with several patients still living. The median was 12 months with a range of from 3 to 28 months. The average duration of life in the "failure" group was 7.2 months with a median of 5 months and a range of from 1 to 34 months.

The longer length of life in the "successful" group seems to attest to the value of castration. We must take into consideration, however, that in the

"successful" group we are dealing with individuals who have had a long duration of disease and whose disease appears characteristically to run a protracted course. This may represent a less virulent disease in "cancer resistant" individuals. The value of castration is best judged by the rate of production of clinical remissions.

Because several patients are still in remission at the time of this writing, a final determination of duration of remission and of life following castration cannot be made. In those patients who obtained remissions the average remission time to date is 10.2 months with the longest being 28 months.

Many authors have questioned the value of irradiation castration.[1, 8, 19] In our series the average length of life after irradiation was 16.5 months compared to 12.1 months after oophorectomy. The average remission time after irradiation was 11.7 months compared to 9.9 months after oophorectomy. These figures attest to the significant therapeutic value of x-ray castration and indicate that adequate irradiation produces sufficient ablation of ovarian function to equal or exceed the results obtained by oophorectomy.

Morphology and Site of Metastases.—We were unable to demonstrate a correlation between success or failure and the site of metastatic or recurrent disease. An exception is the group of patients with massive hepatic or cerebral involvement or both. We have not achieved remissions by castration in these patients. Some success was obtained in patients whose cerebral or hepatic disease was not overwhelming.

Classification of the tumor by cell type or morphology showed no prognostic relation to castration. In this series we were unable to demonstrate a correlation between tumor type and success or failure of castration.

DISCUSSION

The mechanism whereby remissions from mammary cancer are obtained after castration is not completely understood. A clarification of this mechanism should enable the clinician to select those patients likely to benefit from ovarian ablation. In a previous publication,[4] we reported that castration both by operation and by irradiation effectively terminated the estrogen production of the ovary. Other authors[1, 8, 19] have not had uniform success with irradiation castration. Raven[16] and Treves[19] accept estrogen withdrawal as the probable mechanism of regression of mammary tumors following castration. These authors and others believe that while the premenopausal patient is often benefited by castration, the postmenopausal patient is helped in only rare instances. Lemon[12] has shown that the ovaries of senile individuals in vitro often have the capacity of estrogen production.

MacDonald[14] concludes that castration achieves its results not by the mere withdrawal of a specific hormone, but by a general change in the endocrine climate of the host. There has been recent experimental evidence to show that estrogens stimulate mammary cancer to flourish by accelerating the activity of the enzyme system of the tumor.[9] Conversely, it is postulated that withdrawal of endogenous estrogen production will slow this enzyme activity. This evidence supports the "withdrawal theory."

It is our belief that castration results in effective palliation by directly removing an important source of endogenous estrogen production. In an attempt to find the common denominator between success and failure following castration, we have analyzed our patients in regard to estrogen excretion before and after castration. Determinations of the estrogen excretion were made by bioassay after the method of Smith and Smith[17] and by chromatography utilizing the methods described by Zaffaroni[20] and Bloch.[15] Some patients had Mack stains of the vaginal mucosa before and after castration.

Premenopausal Patients.—Thirty-three of our patients were premenopausal. Twenty-six were subjected to oophorectomy and 7 to irradiation castration. Fourteen (42.2 per cent) obtained both objective and subjective remissions and 3 experienced only subjective remissions for a total of 17 remissions (51.5 per cent). Of the patients castrated by operation, 11 (42.3 per cent) had remissions. There were 9 (34.6 per cent) objective and subjective remissions and 2 patients experienced merely subjective remissions. Five of the 7 who were irradiated obtained objective remissions, 6 obtained subjective remissions. In view of the small size of this group, an expectancy of a remission rate of 5 or 6 out of 7 is unwarranted.

All but 1 of the premenopausal patients showed significant estrogen excretion before castration (above 3 μg of total estrogen per day). In those patients in whom a Mack stain of the vaginal mucosa was obtained prior to treatment, the result was positive (2 plus or more) in all. All the premenopausal patients who benefited from castration showed a decided fall in estrogen excretion after castration. We interpret this to mean that essentially all the precastration estrogen excretion in these patients was due to ovarian activity. In the patients whose estrogen excretion did not greatly decrease after castration, we believe that the adrenal glands were the most important source of the estrogen production. None of these patients obtained a remission from castration.

Postmenopausal Patients.—We arbitrarily included in the postmenopausal group (1) those patients who were definitely postmenopausal, (2) those patients whom we considered to be at the menopause as evidenced by infrequent, scattered menstrual periods, and (3) those patients who had undergone a hysterectomy prior to consideration for castration. In all there were 27 of these patients, of whom 19 were definitely postmenopausal. Seven (25.8 per cent) patients had remissions; 6 (22.2 per cent) had objective remissions and 1 patient had only subjective improvement (Table I). Five underwent operative and 2 irradiation castration.

Twenty patients of this group were castrated by operation, 5 of whom experienced subjective and 4 objective remissions. Of the 7 patients who were irradiated 2 obtained objective and subjective remissions.

Of the 19 definitely postmenopausal patients, 2 were irradiated and 17 were operated upon. Five of the 19 obtained both objective and subjective remissions, a rate of 26.2 per cent. These 5 patients were 1, 2, 6, 15, and 18 years past the menopause. All exhibited strongly positive Mack stains before castration and negative Mack stains after castration. In each of the 5, high estrogen excretion was present prior to castration ranging from 3.2 to more than

10 μg of estrogen per day. After castration, estrogen excretion decreased to insignificant levels (less than 1 μg in 4 patients and less than 2 μg in 1 patient).

Of the 20 postmenopausal patients who did not experience either objective or subjective remissions, 14 were truly postmenopausal, 4 were at the menopause, and 2 had undergone hysterectomies. At the time of castration these 20 patients were 1 to 18 years past the menopause.

Failures of Castration.—Of the 60 patients undergoing castration, 36 (60 per cent) experienced neither objective nor subjective remissions and were classed as "failures." Of these, 16 were premenopausal, 14 were definitely postmenopausal, 4 were at the menopause, and 2 had undergone previous hysterectomies (both patients were in their forties). From the viewpoint of estrogen excretion, these patients can be grouped into 3 categories: (1) low estrogen group, patients who had less than 2 μg of urinary estrogen excreted each day prior to castration; (2) high estrogen group without a decrease after castration, patients who excreted at least 3 μg of estrogen each day and whose excretion remained unchanged after castration; and (3) high estrogen group with decrease after castration, patients who excreted at least 3 μg of estrogen each day prior to castration and whose excretion decreased markedly following castration.

Eleven patients with significant estrogen excretion which decreased after castration did not experience remission. We consider patients such as these to have hormonally insensitive tumors and a response to ablative therapy will not occur. These 11 patients represent approximately 18 per cent of our cases. Only 3 of them were postmenopausal; the rest were premenopausal. The preponderance of premenopausal patients suggests that in postmenopausal patients with significant estrogen excretion, the likelihood of hormonally sensitive tumors is greater than in their premenopausal counterparts. We believe that castration was warranted in these individuals, for we have no certain means of predicting the hormonal sensitivity of a tumor. We will continue to consider such patients as candidates for castration.

There were 14 patients with high estrogen excretion before castration whose estrogen excretion did not decrease after castration. They were evenly divided between premenopausal and postmenopausal women. These patients probably had considerable adrenocortical activity and the urinary estrogen excretion represented not only estrogen produced by the ovaries but also by the adrenal glands. In another publication,[3] we have shown that a high percentage of such individuals eventually benefit from adrenalectomy. In these patients castration did not eliminate the major source of endogenous estrogen production and remission could not be expected. Although we have no certain way of determining the site of origin of estrogen, we have found that patients with high titers of estrone by chromatographic determinations probably will have the estrogen production eliminated by adrenalectomy,[3] while those patients who excrete large amounts of estradiol should have ovarian ablation. These preliminary observations are being amplified at present.

Eleven patients had a low estrogen excretion prior to castration. One patient was premenopausal with a history of irregular menses for many years.

The other 10 patients were either postmenopausal, posthysterectomy, or at the menopause. Castration did not alter the excretion patterns. We believe that in patients such as these the ovaries are biologically inactive and the tumors are flourishing in a medium devoid of estrogen. Ovarian ablation could not lower estrogen excretion and, further, attempts at lowering estrogen excretion cannot be expected to influence a tumor already in harmony with a low estrogen environment.

Individuals who have a low estrogen excretion should not be considered as candidates for castration. In our series, this would have eliminated 11 patients and would have resulted in a remission rate of 49 per cent. In the postmenopausal group, 10 patients would have been excluded to produce a remission rate of 37 per cent.

At the present time, we are unable to eliminate those individuals who have significant estrogen excretion from consideration for castration. We have no method of definitely determining the site of origin of the excreted estrogen and have no means of accurately predicting the hormonal sensitivity of the tumor.

CONCLUSIONS

1. Ablative therapy is indicated only when there is evidence of an active progressive disease that is no longer amenable to local resection or irradiation of a primary, recurrent, or metastatic lesion.

2. Castration offered remission to our patients in approximately 35 per cent of the instances.

3. Castration gave remissions in approximately 40 per cent of the premenopausal patients, and in 22 per cent of selected postmenopausal patients.

4. Castration therapy, when successful, gives remissions for an average of at least 10 months and individual remissions may extend several years.

5. Irradiation castration given in adequate doses effectively ablates ovarian function as shown by remissions and by reduction in estrogen excretion.

6. Postmenopausal patients who show significant estrogen excretion or who have strongly positive Mack stains are candidates for castration.

7. Castration therapy is not indicated for patients who show low levels of estrogen excretion.

8. In our series, all patients who benefited from castration showed a high precastration estrogen excretion that decreased to insignificant levels following castration.

9. Response to castration is a reliable means of predicting the hormonal sensitivity of the tumor in question.

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PROPHYLACTIC BILATERAL ADRENALECTOMY AND OOPHORECTOMY FOR ADVANCED CANCER OF THE BREAST

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THE work of Huggins and his associates[1] and subsequently that of many others has demonstrated that many carcinomas of the breast and their metastases regress or grow very slowly after removal of the ovaries and adrenal glands. Luft and Olivecrona,[2] and others have secured a similar result following either removal of the hypophysis or its destruction by radioactive isotopes. For the most part, these procedures have been employed in patients with mammary cancer when extensive metastases have caused profound deterioration in the patient's condition or have produced intractable pain or invalidism. We have been impressed with the marked palliation we have secured in some patients. Several have survived from 3 to 6 years after bilateral adrenalectomy and oophorectomy when previously they had been incapacitated by metastatic involvement from breast carcinoma. One has been living for over 6 years and is still in apparent good health after having been an invalid with widespread osseous metastases from a breast carcinoma. Two died after 5 years of worth-while palliation. These patients were maintained in excellent health on substitution therapy limited to 37 to 50 mg. of cortisone daily and without dietary modification. Their return to full physical activity was quite remarkable. One patient undertook a transcontinental trip alone by automobile 3 years after removal of the adrenal glands. The emergencies encountered in crossing the Rocky Mountains were surmounted by this lady without difficulty.

The results to be anticipated following radical mastectomy for carcinoma of the breast have become more clear as a result of numerous statistical studies correlated with the presence or absence of metastatic involvement in the regional lymph glands. While 5-year survival may be expected in about 80 per cent of the patients in whom the axillary lymph glands are demonstrated to be free of disease, when carcinoma is found in these glands, the survival rate falls to approximately 20 per cent. When only 1 or 2 of the axillary glands are involved with carcinoma, the outlook is definitely better than when 50 per cent or more of the glands are involved. The histologic appearance of the neoplasm also provides dependable information on the probability of survival after radical mastectomy. When microscopic examination indicates that the

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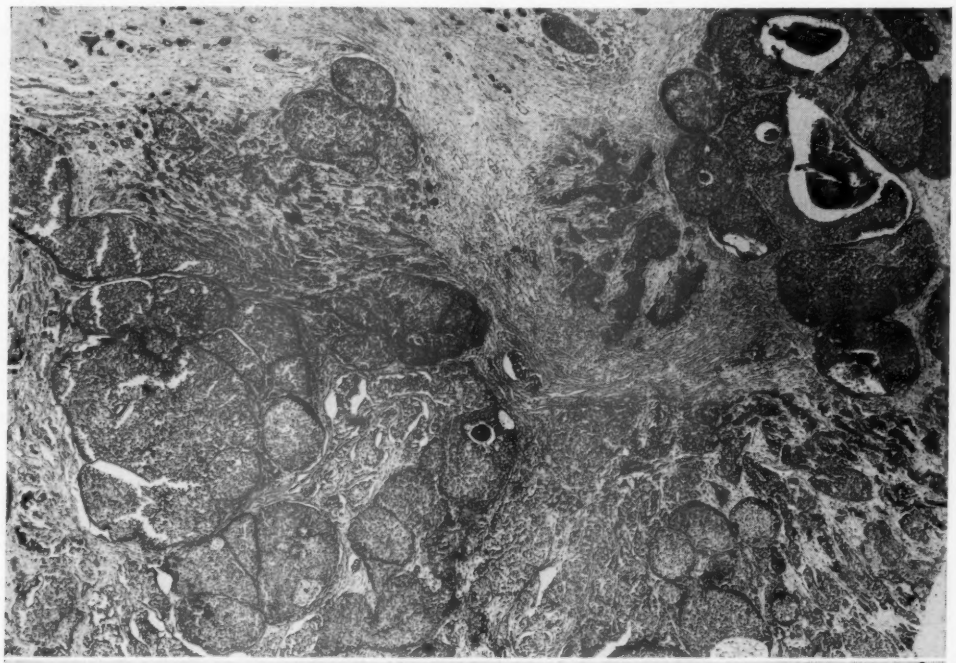
tumor has penetrated the lymphatic vessels, the subcutaneous tissue, and the skin, and if the majority of the axillary glands are involved with carcinoma, the chance of 5 years' survival becomes exceedingly small.

The beneficial effect secured by the removal of hormones from the adrenal glands and ovaries is the result of the withdrawal of the growth and development stimulation these hormones cause in the mammary glands. This effect is also manifested on neoplastic tissue that has not departed too greatly from the tissue of its origin. The effect, however, is not limited to a simple cessation of growth. In many cases marked regression in the neoplastic tissue is a striking feature. It would seem wise, therefore, to take advantage of these effects at the earliest moment that irremovable metastases are demonstrated. Is it justifiable to carry out adrenalectomy and oophorectomy when distant metastases have not been demonstrated but are very probably present?

The condition of patients with widespread carcinomatosis, who have experienced palliation after the removal of the ovaries and adrenal glands, deteriorates quite rapidly when growth in the dormant metastases is resumed. Apparently malignant cells have developed that can grow rapidly in the absence of ovarian and adrenal tissue. The situation may be similar to the appearance of antibiotic-resistant microorganisms in cultures which are held in check for varying periods by streptomycin or other antibiotics. These resistant organisms appear to be mutants that can survive in the presence of the antibiotic or may even require it for satisfactory growth. Perhaps the period of palliation in patients with metastatic carcinoma of the breast is determined by the appearance of mutant cancer cells that can grow in the absence of the hormones from the ovaries and adrenal glands. If this is true the opportunity for the development of such mutants should be much greater when a large mass of carcinoma cells is actively dividing than when metastatic islands are of microscopic size. Removal of the ovaries and adrenals at the earliest possible moment should, on this basis, prolong the period of palliation and might even prevent the appearance of mutant cancer cells.

Restriction of adrenalectomy and oophorectomy to a palliative measure in far-advanced carcinoma of the breast was initially adopted because of reluctance to carry out a radical procedure with a possible high mortality rate, except in patients where palliation could not be secured in other ways. With increasing experience, however, it has become evident that bilateral adrenalectomy can be performed with a very low risk in patients in reasonably good physical condition. Substitution therapy has proved both simple and effective and has produced little disturbance in the customary activity of the patient. Death from carcinoma of the breast usually occurs when a sufficient amount of tumor tissue has accumulated in the body. Contemplation of these facts brought us to the point of view exemplified by the patient to be described in this paper. We were persuaded by the microscopic appearance of the neoplasm, its highly invasive quality, and the demonstrated involvement of most of the axillary glands that distant microscopic metastases were inevitably present. For this reason, shortly after the patient's recovery from the radical mastectomy, bilateral adrenalectomy and oophorectomy were performed as a prophylactic operation.

Fig. 1.



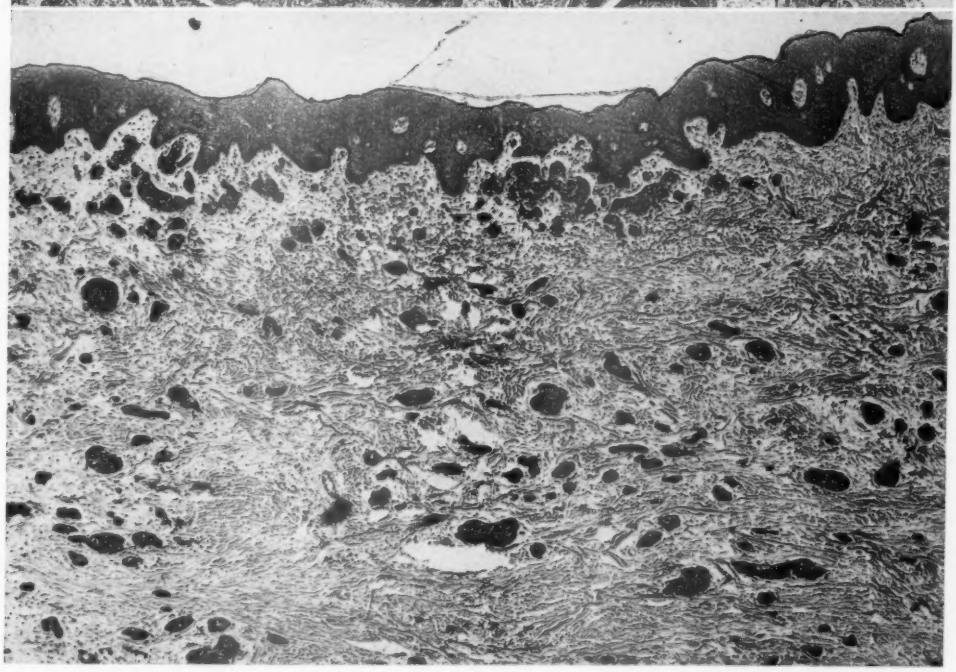


Fig. 2.

Fig. 1.—Photomicrograph from the fibrotic central area of the tumor showing the diffusely invasive character of the carcinoma and the extension into the ducts. There is no uninvolved breast tissue.

Fig. 2.—Photomicrograph from the skin of the breast, in an area with chronic "woody" lymphedema, showing cancer cells in the lymphatics.

CASE REPORT

C. B., a 27-year-old, unmarried, female Negro student, was admitted to The University of Chicago Clinics, Dec. 28, 1951. She complained of a large, hard lump in the right breast. This was first noticed 2 years previously and had gradually increased in size until it occupied most of the right breast. In other respects her health had been good. On physical examination a large, hard mass, 12 cm. in diameter, was found in the right breast. This mass was fixed to the underlying tissue and to the overlying skin. Numerous small, hard lymph glands were palpated in the right axilla. X-ray examination of the chest revealed no abnormalities. A diagnosis of carcinoma of the right breast was made, and on Dec. 28, 1951, a radical mastectomy was performed. Wide excision of the breast left a defect, 6 by 12 inches in size, which was covered by split-thickness skin grafts. The postoperative course was uneventful.

The following report was made by the laboratory of surgical pathology:

"Gross: This radical mastectomy specimen included the usual deep structures; a portion of rectus fascia and muscle; and a large piece of skin, 11 to 20 cm. long and 5 to 15 cm. wide, with the nipple near its center. A hard mass, 7 by 7 by 5 cm., replaces most of the breast tissue. It lies deep to the fixed nipple with a little more of its bulk above than below

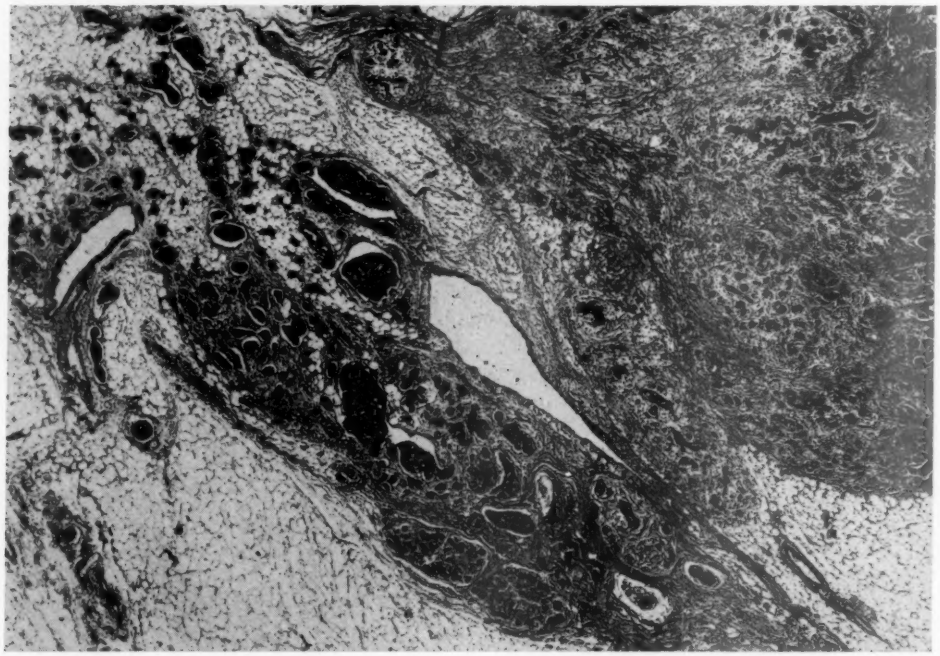


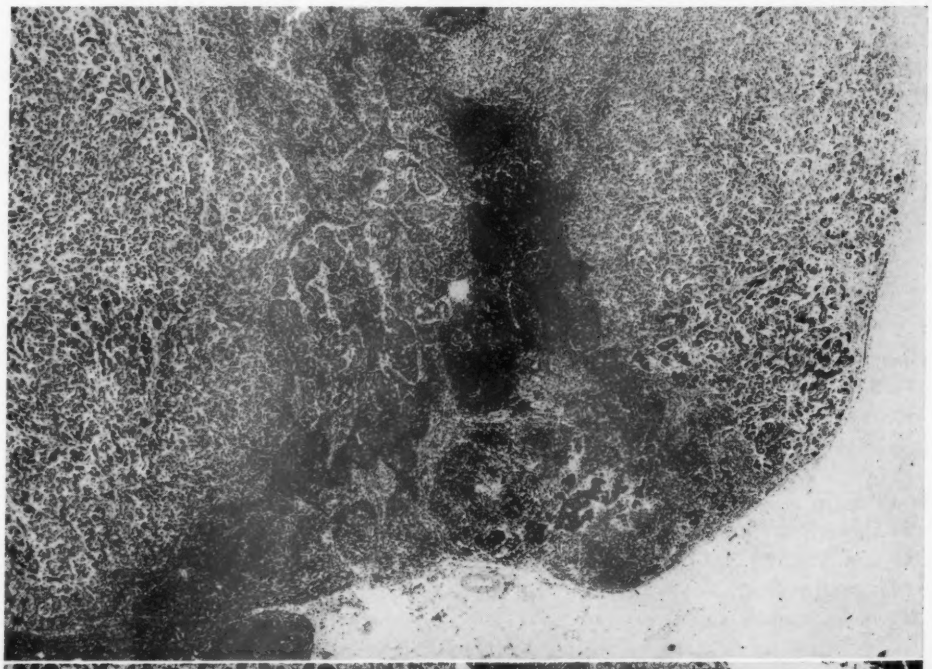
Fig. 3.—Photomicrograph from the margin of the breast showing many lymphatics dilated with cancer cells and also cancer cells in breast and fatty tissue and in the walls of blood vessels. Cancer cells singly and in cords, in small solid nests or acini, permeate the fibrous areas.

that structure. The skin is fixed to the mass over a wide area. There is no visible tumor in the pectoral muscles, but the neoplasm extends to the pectoral fascia centrally, and possibly through it in places. A small hard lymph node is found between the pectoral muscles. The axillary fat contains many lymph nodes, small and intermediate in size. Many of these are hard. On section the gristly hard tumor replaces most of the breast, with a few softer white or yellow and white areas near the nipple, and in the upper outer quadrant.

"Microscopic: The sections demonstrate massive carcinomatosis with large areas of intraductal cancer (comedo type) (Fig. 1), extensive infiltrative growth, and spectacular permeation of mammary and dermal lymphatics (Fig. 2). The lymphatic extensions are of the type and extent to produce the inflammatory cancer picture, were this an early

carcinoma. The comedo units, usually solid but with some gland lumens, often resemble the 'solid' sweat gland tumors of the myoepithelial type. Invasion of fibrous stroma is in the form of thin or broad cords and nests. Some of the tumor thrombi are in hugely

Fig. 4.



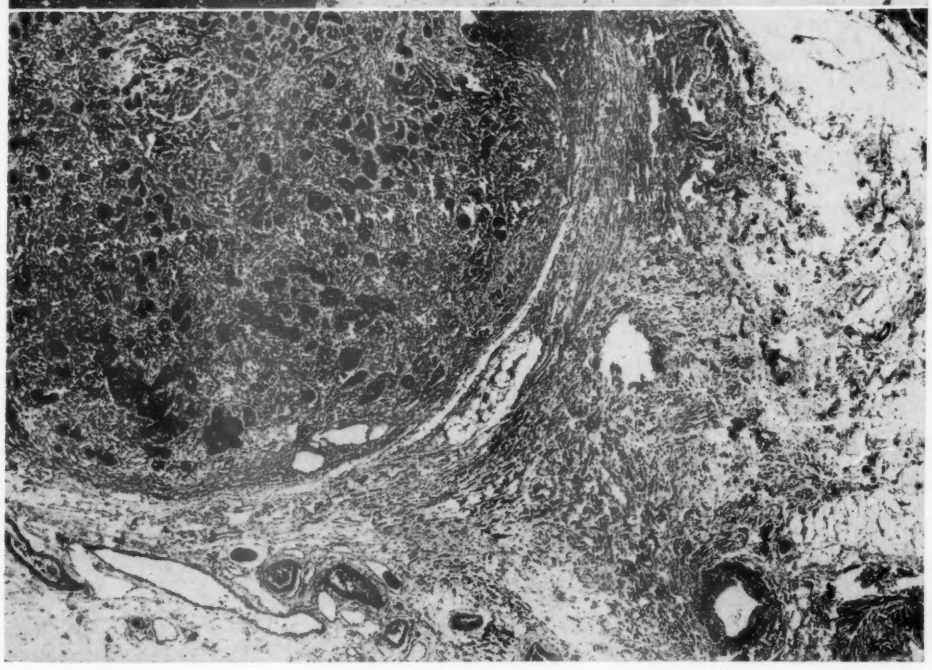


Fig. 5.

Fig. 4.—Photomicrograph from an axillary lymph gland showing cancer cells in the hilar or efferent lymphatics.

Fig. 5.—Photomicrograph from axillary tissue showing extensive involvement of the lymph node, permeation of cancer cells in dilated lymphatics, and diffuse spread of cancer as single cells, cords, or small trabeculae inducing fibroplasia.

dilated lymphatics (Fig. 3). There is much tumor beneath the retracted nipple with lymphatic spread along the large ducts and throughout the areola. Some breast tissue remains inferior to the nipple, adenofibrotic where it is invaded by the cancer cells. Focally this shows adenosis with conspicuous myoepithelium. In a deep superior medial region the carcinoma has reached and grown through pectoral fascia, but not into the muscle. More laterally, above the nipple there is massive carcinomatosis, deep and in the skin, extending to the epidermis. A still more lateral 'control' area displays cancer cells in lymphatics and invading the fat tissue. The breast is focally fibrotic but many lobules are normal. One looks like an area of early lobular carcinoma.

"Fifteen of twenty axillary lymph glands are involved, many being entirely replaced by cancer tissue. Cancer cells also invade the axillary fat and lymphatic vessels (Figs. 4 and 5). The skin margin is free of cancer.

"Pathologic diagnosis: Large mammary cancer, intraductal, infiltrative, and intralymphatic involving skin, pectoral fascia areolar tissues of grossly uninvolved breast, and axilla. Metastases in fifteen of twenty lymph nodes including the interpectoral node."

Because of the findings at operation and particularly because of the nature of the pathologic report, the unfavorable outlook was explained to the patient and further surgery was advised. On Jan. 4, 1952, bilateral ovariectomy was performed. The patient recovered uneventfully and between January 21 and March 3 irradiation therapy was administered over the region formerly occupied by the right breast, the right axillary lymphatics, and the right supraclavicular nodes. To the above sites, 3,900 and 4,100 r, respectively, were given.

On July 17, 1952, the patient returned to the hospital for further surgery. At this time she was in excellent general physical condition, except for the right radical mastectomy scar, the associated areas of grafted skin over the anterior right chest, and the tanning secondary to the irradiation therapy. Bilateral adrenalectomy was performed on July 17, 1952. Recovery from the operation was uneventful, and the patient was discharged in 2 weeks on a maintenance dose of 37.5 mm. of cortisone. She returned to school and resumed her previous activities. During the period between July, 1952, and November, 1958, she was examined in the outpatient department from 4 to 6 times each year. No evidence of recurrence of carcinoma was detected. She is now employed full time as a teacher and when last seen in September, 1959, was in good health and spirit. X-ray examination of the chest failed to reveal recurrence of carcinoma.

SUMMARY

The condition of patients with carcinoma of the breast and widespread metastases, who have secured palliation from removal of the ovaries and adrenal glands, deteriorates quite rapidly when growth in the dormant metastases is resumed. Apparently mutant malignant cells have appeared that can grow rapidly in the absence of the hormones of these glands. Acting on the concept that the chance for mutants to develop would be much greater when large masses of cancer cells are actively dividing than when metastases are of microscopic size, we performed prophylactic bilateral adrenalectomy and oophorectomy in a young woman with cancer of the breast. Radical mastectomy in this patient revealed a highly invasive tumor with involvement of most of the axillary glands and permeation of cancer cells into the lymphatics, blood vessels, and subcutaneous tissue. Distant metastases were not demonstrated but were believed to be present. The patient has remained well without evidence of recurrence and has continued her usual activities for nearly 8 years.

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A TECHNIQUE FOR THE BIOPSY OF INTERCOSTAL PARASTERNAL LYMPH NODES

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IN 1953, McDonald, Haagensen, and Stout[2] suggested that a biopsy should be made of the parasternal intercostal lymph nodes of patients with carcinoma of the breast and that the patients who manifest metastases in these nodes should not be considered for curative radical mastectomy. The indications for such intervention are well documented in Haagensen's monograph, *Diseases of the Breast.*[1] It is beyond the scope of this paper to discuss the merits of the indications or to evaluate the *raison d'etre* of this intervention. It is sufficient to say that the procedure provides a warning sign for the speedy surgeon and cautions him as to the outcome of radical mastectomy.

The usual technique employed in this biopsy procedure is a vertical parasternal approach cutting through the skin, subcutaneous tissue, breast tissue, and the pectoralis major attachments parallel with the skin. We think this technique has some disadvantages and undesirable aspects. First, when a radical Halsted type of incision is preceded by a vertical parasternal incision, a bridge of skin is produced on the medial skin flap. Its blood supply is cut vertically by the parasternal biopsy incision and laterally by the Halsted breast incision. Thus, the already precarious blood supply of the medial skin flap is disturbed. Second, when the vertical incision is used, the underlying tissues are cut through vertically. These are tissues which are an integral part of the excised specimen. Certainly in the surgery of neoplastic diseases entry into the contemplated specimen should be made only when imperative (Fig. 1).

We have devised an operative procedure for removal of the intercostal lymph nodes and have circumvented these 2 disadvantages.

The procedure is as follows:

Position.—Supine. Only the anterior chest wall is prepared for the biopsy.

Anesthesia.—Light, general anesthesia.

Incision and Dissection.—A transverse incision is used, starting in the midsternum and extending into the second intercostal space 6 to 7 cm. The intercostal space chosen might be 1 space lower, depending on which lymph nodes are to be found. The depth of this incision is important. It should never be deeper than the flap thickness of a radical mastectomy which is usually 3 to 4 mm. (Fig. 2).

After this incision is made, the next step is a subcutaneous dissection caudad and cephalad (Fig. 2). Here, too, the raised flaps must be as thin as the contemplated skin flaps in case a radical excision is decided on later. With the

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flaps raised, the medial end of the wound is retracted and the subcutaneous tissues are next incised in the midline on the midsternum. The periosteum is reached for a distance of 6 to 7 cm. (Fig. 3). The breast tissue, pectoralis major fascia, and the muscle attachments on the sternal border and on the second and

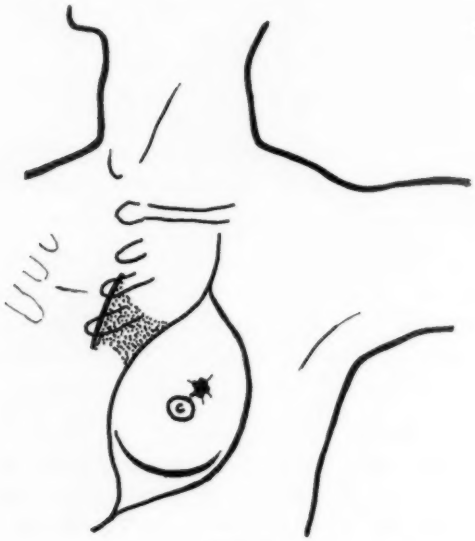

Fig. 1.

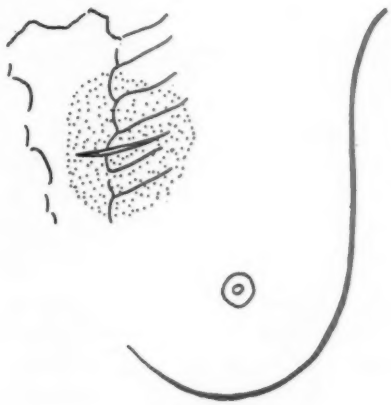

Fig. 2.

Fig. 1.—Cancer of breast in the right upper quadrant. The usual vertical parasternal incision for the intercostal lymph node biopsy and the contemplated Halsted incision. This vertical "supracostal" incision, when employed, will jeopardize the blood supply of the skin flap as indicated by the stippled area. Moreover, the specimen to be removed is cut through unnecessarily, which breaks the code of cancer surgery.

Fig. 2.—The transverse skin incision in the second interspace measures 6 to 7 cm. The stippled area indicates the extent of subcutaneous dissection caudad and cephalad. The skin flaps thus produced must be as thick as the flaps created in the radical mastectomy.

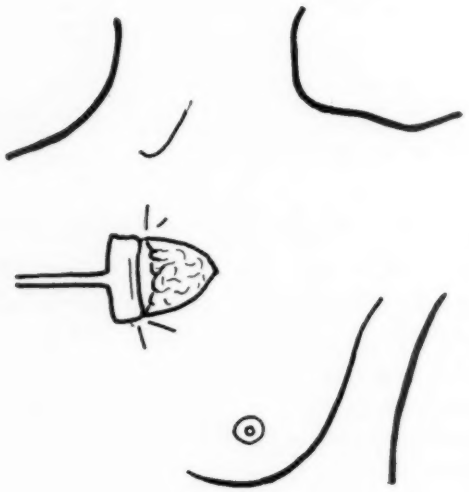

Fig. 3.

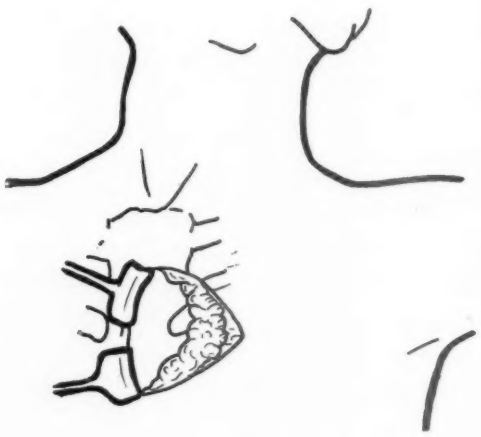

Fig. 4.

Fig. 3.—The medial end of the skin incision is retracted and a vertical incision is made in the midsternum region down to the periosteum.

Fig. 4.—The tongue of breast tissue is elevated and is retracted laterally, exposing the upper interspaces. Any transverse intercostal incision with this approach gives an access to 3 spaces.

third ribs are then elevated. This tongue of tissue, when retracted laterally, gives an entry to the exposed intercostal space (Fig. 4). With this intercostal incision and operative technique, access to the spaces above and below is easily attained.

When the lymph nodes in the space have been removed, the dissected tissues are thoroughly irrigated. Tissues are allowed to fall in gently and carefully together and, if possible, the skin is sutured in 2 layers with fine, nonabsorbable material. If a radical excision of the breast is decided on immediately after the results of frozen section are available, the patient is positioned and prepared anew and redraped. The biopsy wound is cemented and sealed by a rubber dam before the Halsted incision is begun.

It is better to wait for the permanent sections, however, for they afford a safer demonstration of the metastases. If no metastases are seen, this biopsy technique has not violated in any way the precepts of cancer surgery. Then, if metastases are proved, the patient is not operated on.

Drainage.—No drainage is necessary.

SURGICAL CONSIDERATIONS

It is important to remember that the anterior medial portion of the external intercostal muscle does not contain muscle fibers but is composed of a fine, fibrous connective tissue membrane. The direction of the fibers is from above, downward, and medial. The internal intercostal muscle has muscle fibers anteriorly and these have to be cut and teased, in order to expose the internal mammary vessels. The lymph nodes (or node) lie on the side of these vessels. Sometimes the nodes might be just on the inferior border of the sternum. Occasionally, nodes are absent in the interspace and it is easy by this exposure to inspect the 2 adjacent interspaces. It must be remembered, however, that the internal mammary lymph nodes are usually very small, measuring 1 to 2 mm. in size. Because they are notorious for their resemblance to fat lobules, it is a safe procedure to remove for biopsy all of the "fat lobules" if no definite "lymph nodes" are detected. Injury to the mammary vessels might produce alarming hemorrhage. Therefore due respect must be given to them during the dissection. If the vessels cannot be ligated in the narrow interspace, removal of 1 or 2 costal cartilages will give a good exposure and ample space for ligation. Injury to the parietal pleura has occurred even when the best surgeons were operating. If this happens after the biopsies are obtained one should close the wound, leaving the tongue of breast tissue lying against the perforation in the pleura. If no lymph nodes have been obtained at the time of perforation, it is wise not to continue the dissection but to determine the procedure. After such perforations the thoracic cage need not be drained and there is no need to evacuate the sucked-in air. Serial roentgenograms show rapid absorption. The fine capillary ooze from the costal cartilage, the muscle, or the sternal border can be stopped easily by electrocoagulation. Dr. C. H. Haagensen correctly emphasizes the use of fine instruments and delicate technique in these lymph node biopsies. We have found this advice very helpful, and think that

even the suction tip used by the plastic surgery department is large enough to aspirate an intercostal internal mammary lymph node. Suction of tissues is therefore carried out through the meshes of a wet gauze.

DISCUSSION

The advantages of this technique of intercostal lymph node biopsy are evident. With this approach no unnecessary damage is done to the blood supply of the medial flap. Part of the blood supply of the medial, postmastectomy flap is from the blood vessel anastomosis at the sternum, from the other side. With a vertical parasternal incision the blood supply is completely cut off and the viability of the medial bridge of skin depends on the blood vessels coming superiorly from the clavicular portion and inferiorly from the lower chest soft tissues. Moreover, if the transverse incision is found to be near the Halsted incision, it could very easily be incorporated into the latter (Fig. 5).

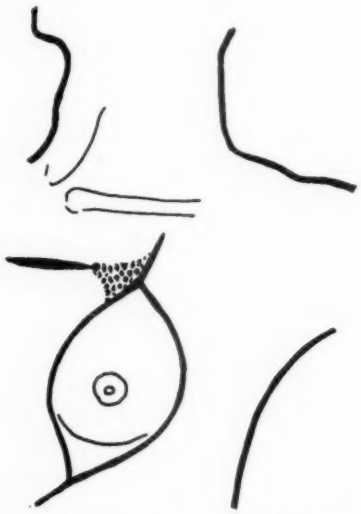

Fig. 5.—When a transverse intercostal incision is performed and a Halsted type of mastectomy incision follows, occasionally the 2 are in close proximity. Here, if desired, the 2 incisions can be made to join, as seen by the extension of the tranverse incision on the stippled area.

The second advantage of such an approach is that it preserves the integrity of the specimen to be removed. The subcutaneous tissues, the breast tissue, and the pectoralis major attachments are excised en bloc without breach of the precepts of cancer surgery.

SUMMARY

A new technique of intercostal node biopsy is described whereby the blood supply to the medial skin flap is kept undisturbed. With this procedure, moreover, the specimen is not cut through unnecessarily, which is in keeping with the code of cancer surgery.

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THE ROLE OF CHEMOTHERAPY IN THE TREATMENT OF BREAST CANCER

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THE past decade has witnessed the development of many compounds with carcinolytic or carcinostatic potential. These include the polyfunctional alkylating agents, antimetabolites, certain antibiotics, steroid hormones, and various other agents. Their use has been reserved largely for far-advanced or hopeless cancer cases. Unfortunately, none of these agents has cured patients with such neoplasms. Growing evidence suggests, however, that properly and carefully managed chemotherapy may help patients avoid a life of incapacitating invalidism for long periods of time. In addition, there is considerable evidence suggesting that chemotherapy combined with surgical procedures may improve the survival rates of patients with early cancer.

Although several polyfunctional alkylating agents seemed promising in the treatment of solid tumors, their value frequently has been limited by toxic clinical side effects in addition to their depressive action on bone marrow. N, N′, N″ triethylene thiophosphoramide or Thio-TEPA, a member of this group, is practically nontoxic clinically and appears to be tolerated by the patient for long periods provided that dosage is adjusted to individual hematopoietic tolerance. This report considers 286 mammary cancer patients treated with this phosphoramide. It includes the cases of mammary cancer reported in 2 earlier articles.[3, 4]

The patients have been grouped as follows: (1) patients with far-advanced metastatic breast cancer (late referrals), (2) patients with inoperable or prognostically poor breast cancer in whom maintenance chemotherapy was started at operation, and (3) patients with early cancer who received only 1 dose or a short course of Thio-TEPA at the time of operation. The observations in each group will be given separately.

OBSERVATIONS

Group 1.—Two hundred and fifty-one women and one man with advanced, uncontrolled mammary cancer are included in this group. Their ages by decades are indicated in Table I. Seventy-six patients were between 40 and 50 years of age and 66 were between 50 and 60. The numbers diminished gradually on each side of this peak. Approximate duration of disease prior to any form of therapy was ascertained and is given in Table II. Although 218 patients received conventional therapy within less than 1 year following discovery of a breast lump, there were 9 cases (3.5 per cent) with disease untreated

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for 5 years or more. Table III indicates the type of mastectomy sustained by 213 patients who were treated primarily by surgical means. Twenty-one women sustained operations for bilateral breast tumors. Table IV shows the types of therapeutic procedures employed in an effort to control cancer prior to the institution of chemotherapy. Resection of tumor, including mastectomy, was performed from 1 to 8 times in 218 patients. Ninety-six patients received

TABLE I. GROUP 1. AGE DISTRIBUTION OF 252 PATIENTS WITH ADVANCED MAMMARY CARCINOMA TREATED WITH PHOSPHORAMIDES

NO.	AGE IN YEARS
3	20-29
29	30-39
76	40-49
66	50-59
46	60-69
19	70-79
13	80-89
Total 252	Average age 54

TABLE II. GROUP 1. ADVANCED OR RECURRENT MAMMARY CARCINOMA TREATED WITH CHEMOTHERAPY IN 252 CASES

DURATION OF DISEASE PRIOR TO ANY FORM OF THERAPY	NO.
1 yr.	218
1-2 yr.	16
2 yr.	5
3 yr.	3
4 yr.	1
5 yr.	4
6 yr.	1
7 yr.	2
9 yr.	1
10 yr.	1
Cases of untreated disease over 5 years' duration	9 (3.5%)

TABLE III. GROUP 1. TYPES OF MASTECTOMY IN 213 PATIENTS WITH MAMMARY CARCINOMA SUBSEQUENTLY TREATED WITH CHEMOTHERAPY

MASTECTOMY	NO.
Simple*	
Unilateral	19
Bilateral	1
Radical	
Unilateral	173
Bilateral	15
Simple and radical	
Bilateral	4
Local resection and radical	
Bilateral	1

*Patients who had a simple mastectomy followed by radical surgery of the same breast are listed under radical mastectomy only.

postoperative x-ray therapy. One to 5 courses of x-ray for metastatic disease were administered to 129 patients. Forty-eight patients were castrated, 32 by operation and 16 by x-radiation. Other forms of therapy included radium plaques, Au^{198}, estrogens, testosterone, adrenalectomy, cortisone, propylthiouracil, TEM, HN_2, and "vaccine" therapy.

Thio-TEPA,* obtained in crystalline form, was dissolved, 10 mg. per cubic centimeter, in pyrogen-free water, sterilized by passing through a Seitz filter, and stored under refrigeration. Nine patients treated with a closely related phosphoramide compound, N-(3-oxapentamethylene)-N′, N″ diethylenephosphoramide (ODEPA), are included. Twenty-seven other patients received ODEPA as a substitute for Thio-TEPA during short intervals. Because the actions of Thio-TEPA and ODEPA are similar except for the greater hematologic toxicity of the latter, no attempt has been made to separate these patients.

TABLE IV. GROUP 1. PRIOR THERAPY IN 252 PATIENTS WITH ADVANCED MAMMARY CARCINOMA TREATED WITH THIO-TEPA

THERAPY	NO.	THERAPY	NO.
Surgery		Radium	
Biopsy	43	1 time	1
		2 times	1
Resection			
1 time	163	AU^{198}	4
2 times	43		
3 times	6	Estrogens	
4 times	2	For primary	4
5 times	3	For metastases	38
8 times	1	Testosterone	64
		Oophorectomy	31
X-ray		Orchiectomy	1
Postoperative	96	X-ray castration	16
Courses		Adrenalectomy	3
1 time	81	Cortisone	2
2 times	23	Prophylthiouracil	1
3 times	18	TEM	1
4 times	5	HN_2	4
5 times	2	Vaccine	1

TABLE V. GROUP 1. DOSE SCHEDULE OF THIO-TEPA IN 252 CASES OF ADVANCED MAMMARY CARCINOMA*

ROUTE	INITIAL DOSE	MAINTENANCE	INTERVAL
Local†	30-60 mg.	5-50 mg.	1-4 weeks
Intravascular	20 mg.	5-25 mg.	1-4 weeks
Oral	5 mg.	—	1-7 days

*Nine patients received ODEPA only. In 27 cases ODEPA was used as a substitute for Thio-TEPA during short intervals.

†Includes intratumor, intracavitary, and transhepatic routes.

Total dose of phosphoramide ranged from 35 to 1,897 mg. (average 455 mg.), and duration of treatment ranged from 0.2 month to over 4 years (average 9.3 months). The drug was given by the intratumor, intrapleural, intrapericardial, intraperitoneal, intravenous, intracarotid, and oral routes as indicated in Table V. The attempt was made to accumulate as much drug as possible at the tumor site which posed the greatest threat to the patient. Pulmonary and intracranial metastases were treated by intravenous administration of drug and intracarotid injection was employed in a few of the latter cases. Intramuscular injection was used for a short time in 1 patient only. Oral drug was given in capsule form in order to maintain therapy during vacations in a few cases. Because the leukocytes had been found to be the blood elements which were affected earliest, a white blood count was obtained prior to each parenteral treatment

*Furnished by Lederle Laboratories, Division of the American Cyanamid Company.

and its level guided all but the initial dose of drug. Therapy was administered at weekly intervals until the neoplastic process showed signs of regression or control. The interval was then gradually lengthened. With few exceptions, intervals longer than 3 to 4 weeks seemed undesirable.

Supplementary therapy (Table VI) with steroid hormones was employed in the presence of inanition and for hematopoietic depression. A combination of small doses of cortisone and a long-acting adrenocorticotropic hormone appeared to be more effective than other related steroids. Three patients received some form of estrogen for limited periods with but transient benefit. Blood transfusions were given when the hemoglobin diminished to approximately 7 Gm. per cent with a few exceptions. Vitamins, except ascorbic acid, were given only for specific deficiencies. Because of its growth-stimulating potential, vitamin B_{12} was avoided. Mild analgesics such as hydrocodeinone were employed. Morphine and related narcotics were used only during brief terminal episodes. Tranquilizing agents in small doses were frequently helpful and appeared preferable to the barbiturates. X-ray therapy was employed usually for localized bone lesions and in a few cases for primary inoperable breast tumors in conjunction with chemotherapy. When metastatic brain lesions could be localized by the neurologist, local x-radiation was combined with intravenously administered Thio-TEPA.

TABLE VI. GROUP 1. SUPPLEMENTARY THERAPY IN THIO-TEPA-TREATED PATIENTS

Steroid hormones for inanition and poor hematopoietic state
Cortisone 10 to 25 mg. postoperatively, twice daily
Long-acting ACTH 40 units intramuscularly 1-2 times weekly
Estrogens occasionally for ulcerated lesions in elderly females
Vitamins (except C) only for specific deficiencies (B_{12} avoided)
Mild analgesics (dehydrohydroxycodeinone) and tranquilizing agents
X-ray therapy for localized bone lesions and in a few cases for primary inoperable breast tumor

If therapy was started during a hospital admission every effort was made to ambulate and discharge the patient as rapidly as possible and treatment was continued on an outpatient basis as long as possible. Subsequent hospitalization was reserved for treatment of complications or short terminal episodes.

Symptomatic improvement was the rule rather than the exception and was frequently dramatic. However, because of the known profound psychologic effect that a positive approach to a frightening illness may evoke, subjective improvement is difficult to evaluate. For this reason, objective response and survival time have been used as criteria for the evaluation of chemotherapy in this series.

Types of objective improvement achieved are listed in Table VII. Regression of disease by the criteria noted ranged from mild to complete. Of 35 patients whose primary tumor had not been removed for reasons of inoperability or distant metastases (13 patients), or in whom there was reactivation following x-ray (19 patients) or hormone therapy (3 patients), 22 or 63 per cent demonstrated varying degrees of regression. Metastases to the opposite breast regressed in 18 of 33 cases. Improvement was noted in approximately ⅔ of

those treated as judged by regression of ulceration and inflammatory spread, diminution in size of nodes and subcutaneous nodules, and disappearance of central nervous system signs. Although objective regression of osseous metastases was seen following institution of therapy with Thio-TEPA alone, this required 2 to 4 months before it could be demonstrated by x-ray. Supplemental x-ray therapy has been used largely for localized metastatic bone lesions in the majority of our later cases. Administration of Thio-TEPA was continued during the period of irradiation and the possibility that it contributed to control of the osseous lesion must be considered. In some cases injection of Thio-TEPA at the site of a bone lesion resulted in marked relief of pain. Regression of pulmonary metastases was seen only in the nodular type. Regression of signs and symptoms (including jaundice) of hepatic metastases occurred only after injection into the liver. Palpable abdominal masses regressed in 2 of 6 instances. Facial edema secondary to huge cervical node metastases regressed in 3 cases

TABLE VII. GROUP 1. TYPES OF OBJECTIVE RESPONSE TO THIO-TEPA IN 252 CASES OF ADVANCED MAMMARY CANCER

NO.	SITE OF LESION	REGRESSION OF TUMOR	PER CENT
35	Original breast	22	63
33	Contralateral breast	18	54
44	Ulceration	33	75
13	Inflammatory	9	69
93	Nodes	56	60
90	Subcutaneous nodules	58	64
90	Osseous	30*	33
50	Lungs	12†	25
27	Brain	16	60
42	Liver	7	17
71	Pleural effusion	54	76
2	Pericardial	2	100
5	Ascites	2	40
6	Abdominal masses	2	33
4	Facial edema	3	75
1	Jaundice	1	100
2	Uremia	0	0

*Supplemental irradiation to bone lesions given in many cases. The latter are listed as "no response" to Thio-TEPA.

†Response seen in nodular but not lymphangitic pulmonary metastases.

while a fourth patient with this complication was considered inadequately treated. Uremia following testosterone administration which was present at the institution of chemotherapy in 2 cases was irreversible and fatal.

Serous cavity effusion was well-controlled when caused by pericardial or pleural metastases and was less well-controlled when associated with intra-abdominal disease. Table VIII lists the incidence of pleural effusion in 252 patients with advanced mammary cancer. This was bilateral in 6 cases, unilateral in 65. Fluid accumulation (Table IX) was controlled for periods of 1 month to more than 4 years in 52 patients, 6 of whom had 2 separate episodes. In 35 patients control of effusion was terminated by death, 7 individuals were lost to follow-up, and 4 patients are living with no reaccumulation at 2, 27, 35, and 40 months. No control was achieved in 16 patients, 10 of whom were considered in a terminal condition, 1 of whom had received inadequate dosage, and unilateral control was achieved in one. Fluid accumulation was

slowed in 3 cases. From 1 to 6 taps, following which drug was injected, were required to achieve control. One patient previously treated with Au^{198} required 20 taps with subsequent drug injection.

Survival time of 227 patients who died or were lost to follow-up averaged 9.0 months and ranged from 0.2 to 50.2 months (Table X). Two patients

TABLE VIII. GROUP 1. PLEURAL EFFUSION SECONDARY TO MAMMARY CARCINOMA TREATED WITH THIO-TEPA IN 71 CASES

EFFUSION	NO. OF PATIENTS
Bilateral	6
Fluid formed while on Thio-TEPA by route other than intrapleural	9
No control	16
Accumulation slowed	3
Number of taps to achieve control:	
1	25
2	15
3	7
4	3
5	5
6	2
20	1

TABLE IX. GROUP 1. DURATION OF CONTROL OF PLEURAL EFFUSION IN 52 CASES*

NO. OF MONTHS	NO. OF CASES
1.0	6
1.5	4
2.0	7
2.5	2
3.0	11
3.5	1
4.0	4
5.0	3
7.5	1
8.0	1
9.0	1
10.5	1
11.0	1
12.0	2
13.0	1
15.0	2
16.0	1
23.0	1
25.0	1
27.0	1
29.5	1
34.0	1
35.0	1
36.0	1
40.0	1
50.0	1

*Two episodes in 6 cases.

who died in 0.2 months and 11 who died from cancer within 0.5 months following institution of chemotherapy were included. Because response to Thio-TEPA is slow, patients who die in the first month of therapy probably should not be considered in the evaluation of results. The 25 patients living at the time of writing have survived an average of 14.3 months.

Percentage of survival from the time of demonstration of distant metastases in 231 of the patients included in this group who received subsequent chemotherapy was determined by the cumulative Life Table Method as described

by Cutler and Ederer.[7] The data were then compared to those of Connecticut State.[11] Even though chemotherapy frequently had not been instituted immediately following demonstration of distant metastases, the survival times of the chemotherapeutically treated patients were increased two- to threefold after 3 months (Table XI). This improvement probably is seen better in Fig. 1, which gives a semilogarithmic plot of survival times in these 2 groups.

One hundred and ninety patients were followed until death. In 2 the immediate cause of death was septicemia related to drug-induced leukopenia. In 1 of these patients there was no demonstrable cancer at the time of postmortem examination. This was also true in the 1 patient who died of pulmonary tuberculosis. Nine patients died of cardiovascular disease and 3 died of uremia (associated with testosterone therapy in 2 and cause undetermined in 1). There were 3 deaths from homologous serum jaundice. In a fourth patient jaundice was thought possibly to be associated with administration of a phenathiazene drug. One death resulted from bronchopneumonia, 2 patients died

TABLE X. ADVANCED MAMMARY CARCINOMA SURVIVAL TIME FROM INSTITUTION OF CHEMOTHERAPY WITH THIO-TEPA (GROUP 1 PATIENTS)

NO. OF CASES		SURVIVAL TIME IN MONTHS	
		AVERAGE	RANGE
Total	252	9.3	0.2-50.5
Died or lost (37)	227	9.0	0.2-50.5
Living	25	14.3	1.5-47.0

TABLE XI. GROUP 1. PERCENTAGE SURVIVAL FROM DIAGNOSIS OF DISTANT METASTASES IN 231 PATIENTS WITH MAMMARY CARCINOMA WHO RECEIVED CHEMOTHERAPY AT SOME TIME AS COMPARED TO NONCHEMOTHERAPY-TREATED PATIENTS (CONNECTICUT)

	3 MO.	6 MO.	1 YR.	3 YR.	5 YR.
Bateman	93.0	83.0	58.0	16.0	6.0
Connecticut[11]	62.3	43.7	27.8	6.8	1.6

postoperatively, and 1 died with a subdural hematoma. Six patients succumbed to a second concurrent neoplastic disease (3 large bowel, 2 cervix, 1 vulva). One hundred and sixty died presumably from uncontrolled cancer. At postmortem 9 of these patients demonstrated severe postradiation pulmonary fibrosis.

Because maintenance therapy with Thio-TEPA results in amenorrhea and menopausal symptoms it was considered of interest to review the status of the ovaries in 65 patients who came to autopsy. In 13 the ovaries had been removed by operation. Metastatic tumor was present in 10 patients (19 per cent) and in 5 of these it was bilateral. Ovarian metastases, however, were always part of a widespread neoplastic process which refutes the occasionally recommended oophorectomy to remove such metastases by surgical methods. In 32 patients (61 per cent) the ovaries were reported as atrophic. Eight of these patients had had x-ray castration and/or testosterone. Nine of those remaining were under 50 years of age.

Group 2.—In 17 patients with advanced cancer and a poor prognosis, chemotherapy with Thio-TEPA was started at operation or shortly thereafter and was subsequently maintained. There was gross evidence prior to operation of metastases to lung in 3, bone in 2, liver in 1 and in 7 patients the primary

tumor was ulcerated. All patients except 1 had extensive demonstrable regional node involvement. Surgical procedures consisted of radical mastectomy in 8 patients, simple mastectomy in 8 patients, and local excision of a 20 cm. heavily infected ulcerated mass in a single case. In 2 cases 60 mg. of Thio-TEPA was sprayed into the surgical site immediately prior to closure and in 5 others drug was injected under the breast several hours prior to operation.

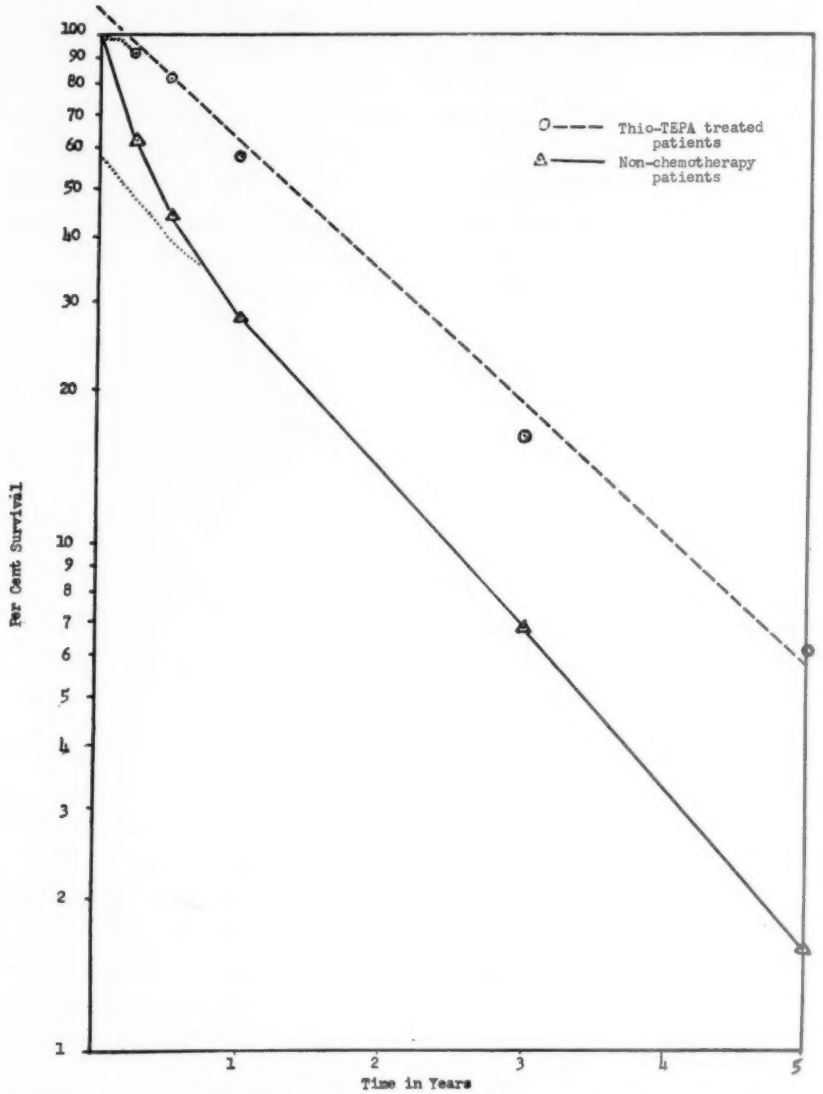

Fig. 1.—Survival time of patients with mammary carcinoma following demonstration of distant metastases. Two hundred thirty-one patients who received varying amounts of Thio-TEPA for advanced or recurrent mammary carcinoma are represented by cross-hatched line. Patients represented by solid line were treated by conventional methods only (data from Connecticut State Statistics[11]).

Three patients received their first injection of drug 7, 8, and 10 days prior to operation. The remaining 7 patients were started on maintenance chemotherapy 3 to 60 days postoperatively. In all cases good wound healing resulted. Five patients were maintained on oral drug for prolonged periods. The latter

route had the disadvantage that in 1 instance, and possibly in 2, the patient was suspected of not taking all the medication given her. Otherwise, when no palpable or visible disease existed, Thio-TEPA was administered by the intravenous route. Two patients received intrapleural injection of drug for a complicating effusion. The total drug given in this group of cases ranged from 60 to 2,395 mg. with an average total dose of 982 mg. Therapy was managed satisfactorily on an outpatient basis and patients were seen from 1 week to 6 month intervals. The longer intervals were permitted for patients on oral therapy but may not be desirable because of patients' occasional laxity in taking drug.

Two patients died in the postoperative period, 1 from a pulmonary embolus and the other in cardiovascular collapse. The latter also had a severe leukopenia (white blood cells 400) which was attributed to delayed excretion of drug secondary to hypotension during operation and poor renal function. The leukopenia was not considered as a factor in this patient's death because she showed no evidence of infection. Subsequent patients with poor cardiovascular status were given only 40 mg. of Thio-TEPA at the time of operation to avoid this degree of leukopenia. Ten patients died in 1.5 to 37.0 months (average 16.4 months) following operation and institution of chemotherapy. (This includes the 2 patients who probably had not taken their oral drug as prescribed.) Five individuals are alive with no evidence of disease at 9, 19, 30, 42, and 50 months, respectively.

In all cases there was good wound healing and no recurrence of ulceration. There was disappearance of an osteolytic rib lesion in 1 patient and regression of pulmonary metastases in another. Fourteen patients were returned to full activity. The improvement in psychological state by the removal of a large ulcerated tumor was marked.

Group 3.—Chemotherapy with Thio-TEPA for wound sterilization at the time of mastectomy was employed in 17 patients. Radical mastectomy was performed in 15 cases and simple mastectomy in 2. Regional nodes were negative for cancer in 14 instances while 3 patients had 1 or more positive nodes.

A single dose of 40 to 60 mg. of Thio-TEPA was sprayed or injected into the wound immediately prior to closure in 11 cases. A total of 80 to 115 mg. was administered locally in 3 or 4 doses to 4 patients over a period of 4 to 15 days starting at the time of operation. Two other patients received a total of 60 mg. by the intravenous route in 3 divided doses over 4 to 6 days.

In 15 patients there is no evidence of recurrence in 3 to 33 months (average 19.3 months). One patient developed a local recurrence at 21 months. Another patient died at 5.5 months with massive hepatic metastases. In the latter 2 cases axillary nodes were negative for cancer at the time of operation.

DISCUSSION

As long ago as 1931 the carcinolytic action of sulfur mustard on human tumors was demonstrated by Adair and Bagg.[1] Interest in the compound waned until World War II. Since 1946 a voluminous literature has accumulated on the countless cytotoxic agents which have been synthesized and given animal

and clinical trials. The polyfunctional alkylating agents, of which nitrogen mustard (HN_2) is a prototype, form probably the largest and most promising group. HN_2 has been reported of value in the control of serous cavity effusion of neoplastic origin.[5] The effectiveness of Thio-TEPA in the control of advanced metastatic breast cancer has been reported by Watson,[20] Humphrey,[12] Davis,[8] Wright,[22] and Moore.[17] It is unfortunate that the latter 2 observers list as failures the treatment of many patients who were either obviously undertreated or followed for too short a period for improvement to become manifest. Wright's "failures" include the treatment of 4 patients who received a total dose of only 10 mg. of Thio-TEPA and that of 7 patients who died in 20 days or less following institution of chemotherapy. Ten of Moore's 33 patients lived less than 1 month. Thio-TEPA is a slow-acting drug. Visible regression of disease is unusual in less than 3 to 4 weeks.

Even if Thio-TEPA were not as effective as other agents in the control of effusion secondary to pleural metastases in mammary cancer, the ease of administration and lack of clinical toxicity would often warrant its use. Administration of Thio-TEPA can be achieved through the same needle which is used to withdraw ascitic or pleural fluid. The procedure is managed conveniently in the clinic or office. The duration of control is also impressive. No pleural irritation or "hot spots" such as may occur following nitrogen mustard or Au^{198} injection have been encountered. The slowly crippling side effect from progressive cicatrizing of the serosa following the latter agent not only limits its usefulness if there is a life expectancy of 1 year or more, but also impairs the effectiveness of subsequent chemotherapy. The over-all regression in approximately two-thirds of the Thio-TEPA-treated patients exhibiting ulceration, nodes, or subcutaneous nodules secondary to mammary carcinoma was as good as or better than could be achieved with any other modality of therapy. The unfortunate possibility of accelerating disease which exists with the administration of certain types of hormone therapy[14, 21] is not present.

No form of hormone therapy, including hypophysectomy,[2, 15] appears to be effective for hepatic or intracranial metastases in mammary cancer. In an earlier report[3] no regression of hepatic metastases was reported following chemotherapy with Thio-TEPA. Subsequent cases were treated by intrahepatic injection of drug and regression of not only hepatic metastases but also subcutaneous nodules followed. Apparently, as in the case of pleural metastases, local injection of drug is imperative for results. Dramatic regression of cerebral metastases[8] following intracarotid injection of Thio-TEPA has been reported. In our experience intravenous injection of drug at more frequent intervals than employed by Davis is equally effective and considerably less difficult technically. If the metastatic site in the brain can be localized, we have found local x-radiation plus intravenous administration of Thio-TEPA to be the treatment of choice. The same is true for osseous metastases. Injection of Thio-TEPA close to, or at the site of, a bone lesion may result in dramatic relief of pain. We now feel, however, that supplemental local x-radiation produces the best over-all control of this type of lesion.

Nodular lung metastases respond well to intravenous injection of Thio-TEPA. The lymphangitic pulmonary metastases, however, appear to be just as resistant to chemotherapy as they are to hormone or x-ray treatment. Because of the not infrequent severe pulmonary fibrosis secondary to irradiation it well may be that x-ray therapy is undesirable postoperatively as well as for metastases involving the chest. The devastating effects of such fibrosis increase with survival time.

Objection has been raised to the claim that a chemotherapeutic agent is effective when all manifestations of a neoplastic process do not regress equally. Equal, simultaneous regression of metastatic lesions in 1 individual would depend on equal sensitivity of each lesion, equal size of the lesions, and an equal dose of drug delivered to these sites. The latter situation is impossible to achieve largely because of the variability in blood supply to each lesion which probably accounts for much of the variability in response.

The difficulty in evaluating survival time of patients treated for mammary carcinoma is compounded by the impossibility of advance evaluation of the intrinsic malignancy of any one tumor. The multiplicity of factors affecting prognosis has been clearly summarized by Gordon-Taylor,[10] who includes the incalculable factor of the patients' own resistance to cancerous invasion. In our group of patients with advanced cancer it was interesting to find that 3.5 per cent of the patients had had their breast mass for over 5 years before seeking any form of therapy. Small and Dutton[18] pointed out that mortality from cancer is a constant process, little affected by treatment. They further stated that between 24 and 38 per cent of patients with cancer behave as if cured with respect to mortality, regardless of method of treatment. If this is true then it would seem advisable to elect a form of therapy most sparing of the patient's financial, social, physical, and emotional resources. Furthermore, the limitations in evaluations of limited numbers of cases are apparent. It is with appropriate concern, therefore, that we point out the improvement in survival times achieved in this series of cases. The quality of survival time is probably of greater importance than its duration. We consider that quality of survival in these far-advanced cancer patients was good in that none required opiates and that most maintained normal activity or were returned to employment.

The mechanism of action of polyfunctional alkylating agents is beyond the scope of this paper. To say that the rapidly dividing cells are most vulnerable is probably gross oversimplification. Why some tumors such as ovarian and mammary neoplasms tend to be sensitive to Thio-TEPA is no more clear than why all mammary or ovarian tumors with similar histopathologic characteristics are not equally sensitive. The possibility that some of the drug's action may be mediated through its effect on the adrenals or gonads exists. The consistent appearance of menopausal symptoms and cessation of menses in patients on maintenance chemotherapy has been noted. For this reason the autopsy protocols of 65 patients were reviewed with special reference to the status of the ovaries. Atrophy of the ovaries was positively mentioned in 32 cases, and may have been present in more. For these reasons the

procedures of surgical or x-ray castration appear to be unnecessary if chemotherapy is contemplated. From our data it appears that the over-all percentage of remission as well as duration of control of metastatic mammary cancer is greater following chemotherapy than it is with any form of hormone therapy.

Patients are regularly seen with primary far-advanced mammary cancer. Many of these women had previously sought faith healing deliberately, either because of the fear of surgery or because of the poor results of surgery seen in some of their friends or relatives. Our Group 2 included patients in both of these categories. It was gratifying to find that large ulcerated lesions could be resected and good wound healing achieved by the concomitant use of Thio-TEPA. Our observations confirm those of Farhat[9] that Thio-TEPA does not interfere with the healing of wounds. Healing in the presence of residual cancer actually is facilitated by destruction of tumor cells. A combination of limited surgical treatment and chemotherapy in far-advanced lesions permitted minimal hospitalization (1 patient attended a luncheon party less than 72 hours after operation) and postoperative chemotherapy was achieved on an outpatient basis.

Increasing attention is being focused on the probability that cancer cell seeding at the time of operation may be related to treatment failures.[6, 19] The administration of Thio-TEPA reduced the number of metastases in animals given intravenous injections of tumor cells.[13, 16] The use of an agent such as Thio-TEPA for wound and blood sterilization is an exceedingly simple procedure. The most desirable dose schedule requires some time for evaluation. Such a limited procedure should under no circumstances be considered adequate for disease which has already metastasized by the time of operation. A word of caution should also be said in regard to dose. The effectiveness of a drug is proportional to the amount retained in the body. The amount of Thio-TEPA retained appears to be inversely proportional to renal function. The latter factor does not require that elaborate renal studies be made in all cases. It does, however, mean that patients with reduced renal function, which can be assumed in the presence of old age, debility, or chronic cardiovascular renal disease, may be expected to excrete drug more slowly than a normal individual and therefore should be given a smaller total dose than would ordinarily be employed.

Until the ultimate cause and cure of neoplasms are determined, properly applied chemotherapy offers the hope of substantially increased palliation in advanced or recurrent disease as well as an increased cure rate in the so-called early operable tumors.

SUMMARY AND CONCLUSIONS

1. The chemotherapeutic management of 252 patients with advanced mammary cancer is discussed. Maintenance therapy with Thio-TEPA resulted in objective remission of metastatic nodes, subcutaneous nodules, ulceration, inflammatory spread, brain, liver, lung, and bone lesions. Survival rates were increased over those for comparable patients treated in other ways.

2. The simultaneous administration followed by maintenance therapy with Thio-TEPA permitted operation in 17 patients with advanced metastasizing tumors including 7 with tumors which had ulcerated. In all except 2 patients, who died postoperatively, there was good wound healing and minimal morbidity.

3. Prophylactic chemotherapy with Thio-TEPA at the time of operation was employed in 17 cases of presumably early mammary cancer. There has been no recurrence to date (3 to 33 months) in 15 cases. One patient had a local recurrence in 21 months and 1 died in 5.5 months with massive hepatic metastases.

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RADICAL MASTECTOMY WITH CONSERVATIVE ANTERIOR MEDIASTINAL NODE DISSECTION: THE "TRAP-DOOR APPROACH"

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IN spite of better understanding of the lymphatic drainage of the breast and improved technology of surgery with its adjuncts, survival rate of patients with breast carcinoma is distressingly low. This is due in part to the fact that we have a poor understanding of the biologic host-tumor relationship as well as a poor knowledge of the exact mode and extent of the spread of the disease at the time of initial treatment.

Although the fact was well known that the internal mammary lymphatic chain drained the medial portion of the breast, as shown in Gray's *Anatomy* in 1883,[2] as well as Stibbe's[17] comprehensive study in 1918, little attention was paid to this fact by the anatomists or the surgeons. Apparently Cushing was the first to apply surgery to the anterior mediastinal nodes while working as House Surgeon under Halsted. Halsted[4] stated in 1898, "Dr. H. W. Cushing, my House Surgeon, has in three instances cleaned out the anterior mediastinum on one side for recurrent cancer. It is likely I think that we shall in the near future remove the mediastinal contents at some of our primary operations." Although Halsted[5] reported a large series of neck dissections in continuity with the radical breast operation, he never mentioned the internal mammary nodes again in his publications.

The next surgeon who adapted this anatomic knowledge to surgical application was W. S. Handley.[10] In the early 1920's he excised the internal mammary nodes in 5 patients, but abandoned the procedure because "it makes the operation too long and severe." Therefore, he treated the internal mammary nodes in a series of patients with radium tubes inserted in the intercostal spaces. This procedure was not accepted widely but has recently been revived by Hendrick.[11]

R. S. Handley[6-9] further pursued the work of his father and has shown the significance of the internal mammary lymphatic chain and its surgical approach. Following this stimulating study several other articles have been published.[12, 14, 15, 16, 18, 19] Urban[23] has recently reported 300 radical mastectomies with internal mammary node dissection.

This paper deals with only one small facet of the breast cancer problem, namely, the diagnosis and management of metastases to the internal mammary node chain.

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ANATOMY

The internal mammary lymphatic chain lies deep to the costal cartilages as a plexiform structure that surrounds the internal mammary vessels. The entire lymphovascular chain is embedded in soft adipose tissue. The lymph nodes measure a few millimeters in diameter up to 1 or 2 cm. in diameter when involved with tumor. The nodes are occasionally so small that they can be detected only by microscopic examination. Involved nodes may penetrate through the chest wall as palpable nodules in the parasternal area.

The highest frequency of nodes is noted in the second intercostal space. The first and third follow in order (Table I).[13] The lymphatic chain drains the

TABLE I. LOCATION OF INTERNAL MAMMARY NODES[13]

INTERCOSTAL SPACE	TOTAL NODES PER SPACE	AVG. NODE PER SPACE	NO. OF INVOLVED NODES	
			URBAN	HANDLEY
1st	394	1.0	21	13
2nd	439	1.1	33	13
3rd	299	0.8	25	7
4th	108	0.3	12	4
5th	47	0.1	2	—
6th	113	0.4	—	—
		Total cases	93	37

TABLE II. RELATIONSHIP OF INTERNAL MAMMARY NODE AND AXILLARY NODE INVOLVEMENT

	NEG.	AXILLARY ONLY	INTERNAL MAMMARY ONLY	AXILLARY AND INTERNAL MAMMARY	TOTAL
Handley & Thackray[7]	33	34	4	29	100
Handley et al.[9]	19	15	11	12	57
Wyatt[25]	22	19	7	12	60
Urban[22]	103	50	17	65	235
Andreassen[1]	55	25	4	13	97
Total	232	143	43	131	549

anterior chest wall, breast, anterior mediastinum, and possibly the upper anterior abdominal wall and periphery of the diaphragm. The lymph commonly empties into a gland just above the clavicle and then into the subclavian vein.

The communication between the breast lymphatics and the internal mammary lymphatic chain is quite constant. The communicating lymphatic chains run parallel to the vessels in each intercostal space after piercing the pectoralis muscle. They course with the perforators through the intercostal muscles to enter the internal mammary chain. The perforating vessels are largest at the second intercostal space, which correlates with the highest frequency of nodes found in this space.

STATISTICS

When several of the larger series of Handley,[7, 9] McDonald and associates,[15] Urban,[22] Wyatt,[25] and Andreassen and associates[1] are tabulated and analyzed, one finds that there were 174 cases (32 per cent) of internal mammary node metastases out of a total of 549 cases (Table II). When axillary nodes were negative the internal mammary metastases were noted in 43 cases (8 per

cent), but when the axillary nodes were positive the incidence rose to 131 cases (24 per cent). This is depicted in the schematic diagram, Fig. 1. Margottini,[14] in his series of 227 cases, also confirmed this impression. When axillary nodes were negative the incidence of internal mammary node involvement was 5 per cent. When axillary nodes were positive the incidence rose to 27.7 per cent with lateral lesions and 40.5 per cent with medial lesions.

TABLE III. INTERNAL MAMMARY METASTASES ACCORDING TO SITE OF LESION[1, 7, 9, 15, 22, 25]

SITE OF BREAST LESION	TOTAL CASES	CASES WITH INTERNAL MAMMARY NODES INVOLVED	%
Central and medial half	434	171	39
Lateral half	219	37	17
	653		

The incidence of internal mammary metastases according to the primary site of the lesion is shown in Table III. The lesions of the central and medial half metastasized to the internal mammary nodes in 39 per cent of the series,

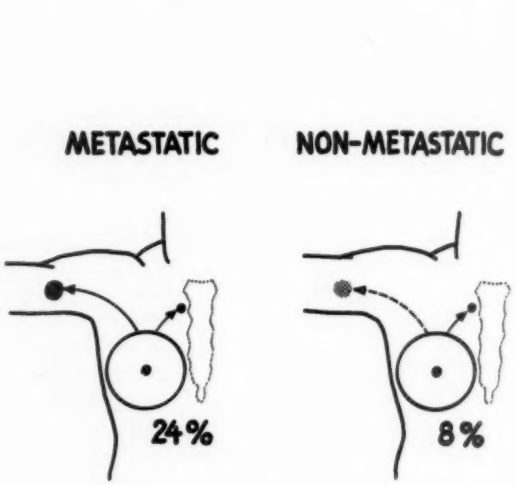


Fig. 1.

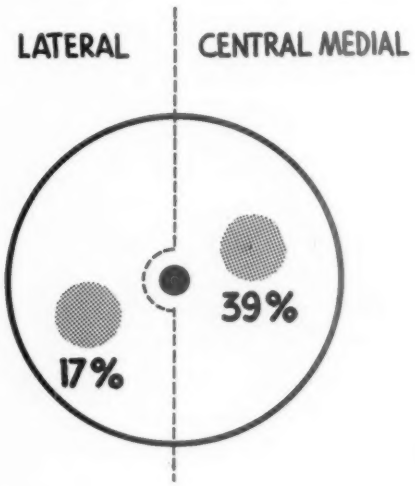


Fig. 2.

Fig. 1.—Relationship of axillary metastases and mediastinal node metastases.
Fig. 2.—Relationship of location of tumor and mediastinal node metastases.

whereas the lateral lesions metastasized in 17 per cent of the cases (Fig. 2). Handley and Thackray[7] have clearly demonstrated that the incidence of internal mammary involvement increases according to the severity of axillary involvement.

There are only 3 cases reported (Handley, Wyatt, and Urban) in which a lateral lesion of the breast metastasized only to the internal mammary nodes without involvement of the axillary nodes.

Several investigators have pointed out that the prognosis of cases with internal mammary node involvement is poor.[7, 23]

TECHNIQUE

En bloc resection in continuity was utilized in the first 7 cases according to the technique described by Urban.[19, 20, 21]

The "trap-door approach," which was utilized in the subsequent 28 cases, will be described in detail. A standard elliptical incision is made well around the tumor (Fig. 3). The superior medial skin flap is raised first and the clavicular and sternal portions of the pectoralis major muscle are separated. The pectoralis major is dissected off the chest wall along the border of the sternum as far laterally as the costochondral junction. This exposes the second, third, and fourth cartilages and their intercostal spaces. The first and fourth intercostal spaces are entered by division of the intercostal muscles transversely. The cartilages of the second, third, and fourth ribs are divided just medial to the costochondral junction along with the adjoining muscle (Fig. 4). The trap door thus created is lifted up with the aid of a gauze and the rib cartilages are fractured at their junction with the body of the sternum. Thus, when the flap is hinged over, the internal mammary lymphatic chain surrounding the internal mammary vessels is seen on the exposed surface (Fig. 5). The internal mammary vessels are ligated and divided just below the first rib and also at the

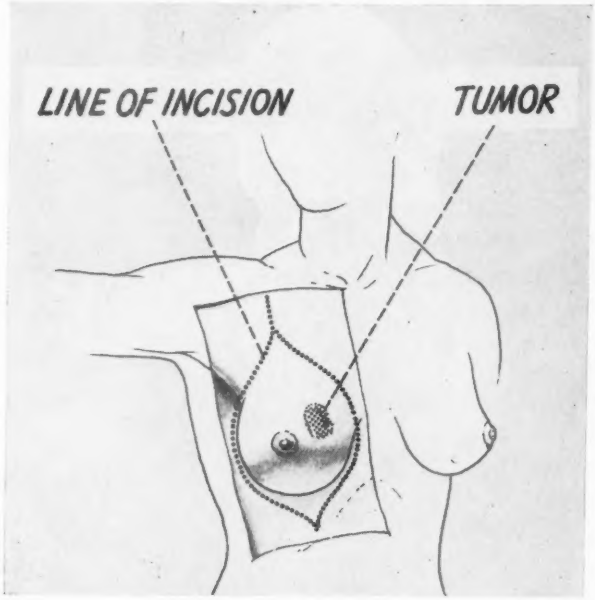
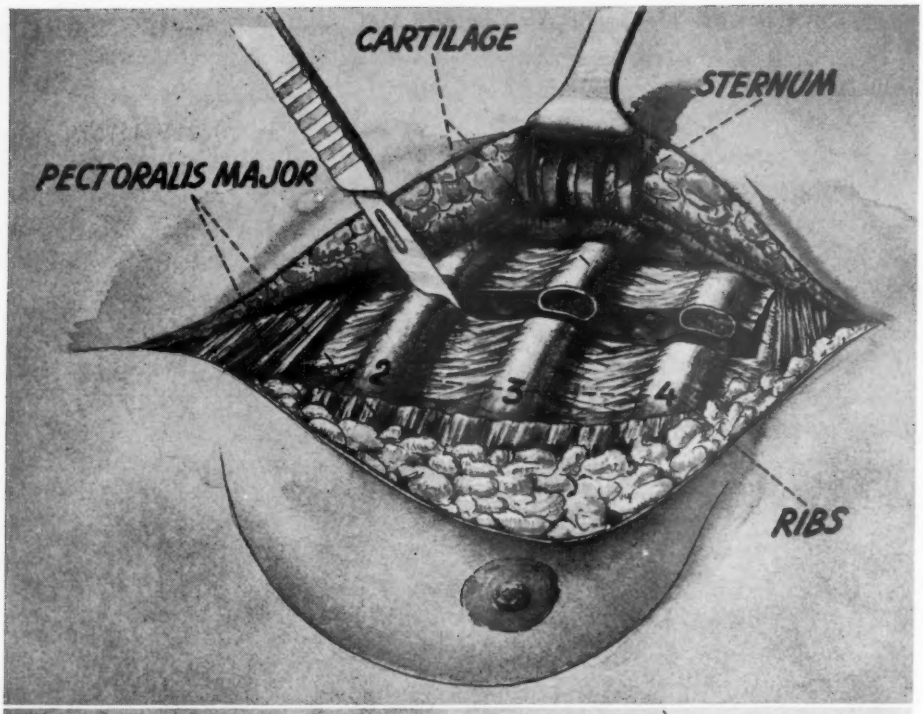


Fig. 3.—Skin incision.

superior border of the fifth rib. The perforating vessels as well as the anterior intercostal vessels are divided and ligated. The entire lymphovascular chain embedded in adipose tissue is resected in continuity (Fig. 6) and sent to the pathologist for permanent section. After the excision of the chain, the trap door is closed with single catgut or wire sutures through each of the cartilages (Fig. 7). The procedure is performed extrapleurally with care. If the pleura is accidentally torn, the opening is closed at once with interrupted sutures. No chest drainage is necessary and postoperative morbidity is extremely low.

The radical mastectomy follows according to the method described by Halsted. This simplified method of removing the internal mammary chain adds less than 15 minutes to the operating time. Some of this time is regained because of decreased blood supply to the remaining operative area.

Fig. 4.



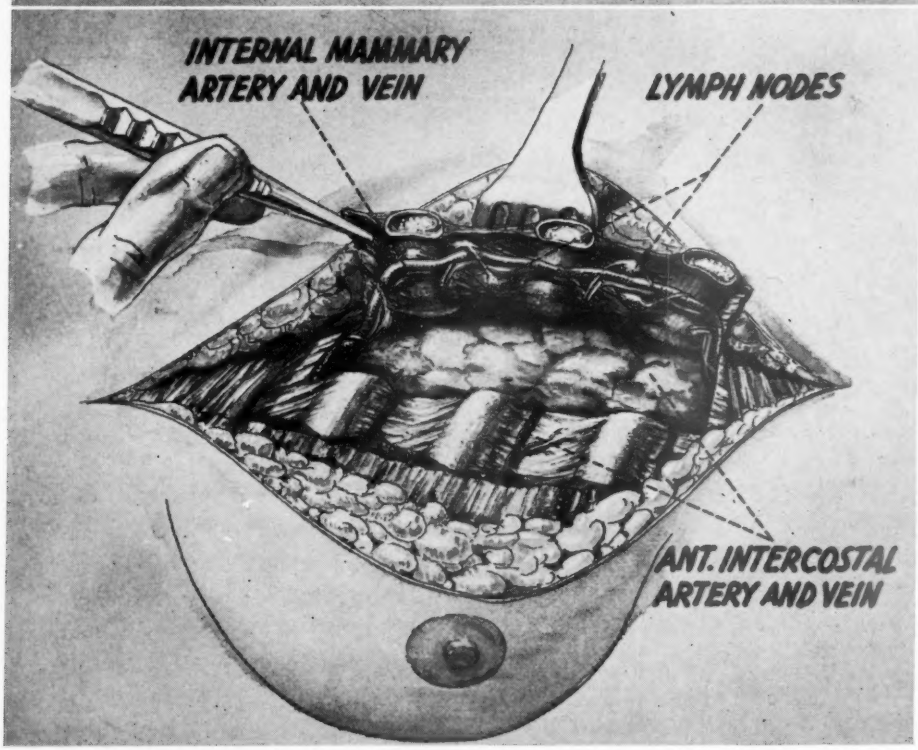
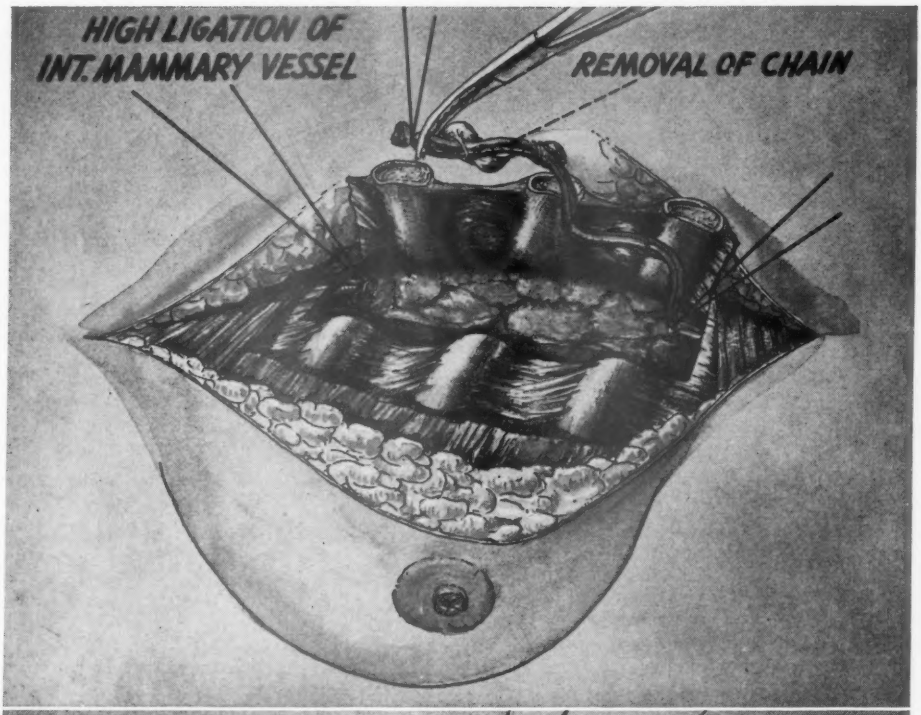


Fig. 5.

Fig. 4.—Division of costal cartilages.
Fig. 5.—The trap door elevated.

Fig. 6.



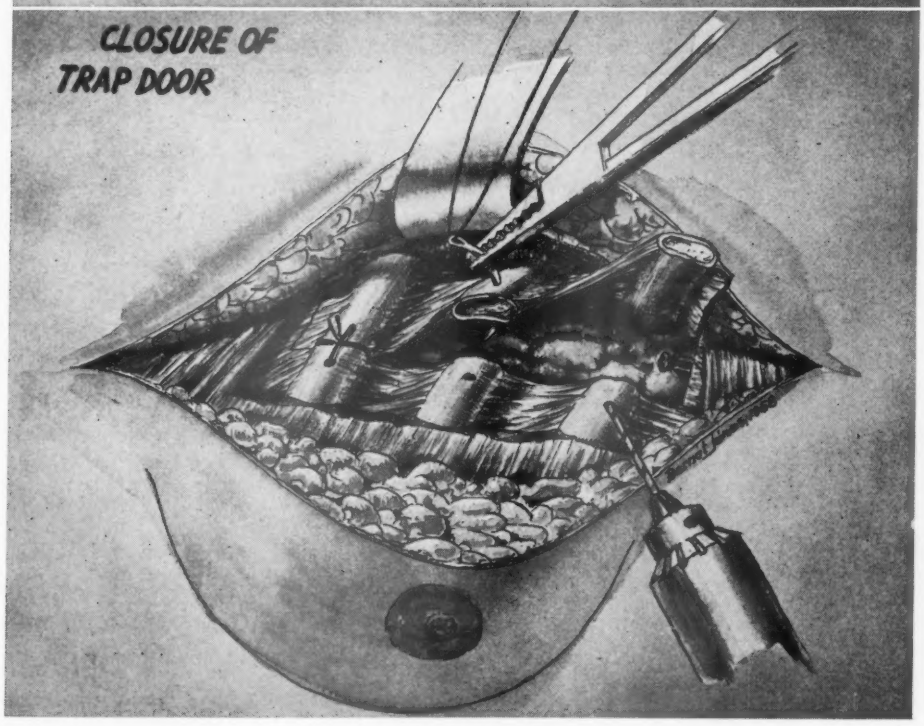


Fig. 7.

Fig. 6.—Removal of the vessels and lymph nodes.
Fig. 7.—Closure of the trap door.

MATERIAL AND RESULTS OF STUDY

A total of 34 female patients and 1 male patient between 29 and 72 years of age underwent the internal mammary node dissection combined with radical mastectomy. The male patient had a malignant melanoma of the skin of the upper chest.

The average hospital stay for the group which underwent en bloc resection was 12 days and for the group with trap-door technique the average stay was 6½ days.

The indications for the extended operation were: (1) medial hemisphere lesions, (2) subareolar lesions, and (3) lateral hemisphere lesions with clinical evidence of axillary metastases.

TABLE IV. LOCATION OF TUMOR AND INVOLVEMENT OF NODES

	NO. OF CASES*	BOTH NEG.	POSITIVE NODES				
			I.M.	AXILLA	BOTH	I.M. ONLY	AX. ONLY
Medial							
Upper	18	7	6	9	3	2	5
Lower	2	0	2	2	2		
Lateral							
Upper	2	2	0	1	1	0	2
Lower	6	1	3	4	3		
Subareolar	7	4	1	3	1	0	2
Total	35	14	12	19	10	2	9

*Right breast, 18, left breast, 17.

TABLE V. FOLLOW-UP OF 35 CASES

1. Positive axillary and internal mammary (10 cases)
   4 patients living and well 6 to 37 months
   1 patient dead
   4 patients living with disease
   1 patient lost to follow-up
2. Positive internal mammary only (2 cases)
   1 patient pulmonary metastases at 12 months, dead at 25 months
   1 patient 4 weeks post operation
3. Positive axillary only (9 cases)
   8 patients living and well 5 to 34 months
   1 patient dead 25 months, widespread metastases
4. Both negative (14 cases)
   All living and well 1 to 40 months

The subareolar lesions were included in this group because the behavior of such lesions is similar to that of the medial hemisphere lesions. There were 20 patients with medial lesions, 8 patients with lateral lesions, and 7 with subareolar lesions (Table IV). There were 12 patients with internal mammary node involvement and 19 patients with axillary node metastases among the 35 patients. Ten patients had both axillary and internal mammary node involvement.

The 35 cases were divided into 4 groups according to the extensiveness of the disease for the purpose of follow-up (Table V). In the first group of 10 patients with positive axillary and internal mammary node metastases, 4 patients have survived 6, 7, 8, and 37 months without recurrence. One patient is dead

at 14 months from widespread metastases. Bilateral adrenalectomy did not alter the course of the disease. One patient is lost to follow-up and is presumed dead. Four patients are living with recurrent disease.

In the second group (2 patients) with positive internal mammary nodes without axillary involvement, 1 developed pulmonary metastasis at 12 months and was dead at 25 months. The second patient was operated on only 4 weeks ago.

In the third group (9 patients) with positive axillary nodes alone, 8 have been living and well for 5 to 34 months and 1 is dead at 25 months with widespread metastases.

When both axillary and internal mammary nodes were negative (14 cases), all patients are living with no evidence of recurrence 1 to 40 months following operation.

COMPLICATIONS AND MORTALITY

The complications are shown in Table VI. Severe chest pain which lasted for several weeks was noted in 2 patients. Without exception the reconstructed ends of the ribs healed without instability. Delayed wound healing due either

TABLE VI. COMPLICATIONS AND MORTALITY

Severe chest pain	2
Delayed wound healing	10
Hemopneumothorax	1
Fluid accumulation under skin flap	5
Pneumonitis	1
Psychosis	1
Glaucoma	1
Total	21
Surgical mortality	0

to infection or to limited skin slough was noted in 10 cases. The rather high incidence of this variety of complication is due in part to the fact that an effort was made to close the wounds without grafting whenever possible. When one partially closes the skin flaps and applies a graft, the area of defect is frequently over the reconstructed ribs, which are a poor base for a skin graft. In such cases it is desirable to swing a flap over the cartilages and graft laterally in a less critical area. In spite of suction catheters placed under the skin flaps, delayed fluid accumulation was noted in 5 instances. These were quite localized and responded well to 1 or 2 aspirations. One case of hemopneumothorax developed as direct result of the surgery which responded well to thoracentesis.

There were no deaths from surgical causes.

DISCUSSION

Of 34 patients with carcinoma of the breast and 1 with malignant melanoma of the chest wall who underwent the usual radical mastectomy supplemented with internal mammary node dissection, the first 7 underwent a block resection in continuity with the radical mastectomy. The trap-door approach was developed in an attempt to simplify the procedure and reduce the morbidity. In comparing the period of hospital stay after the en bloc dissection with that

following the simplified trap-door approach, we have found that the morbidity and hospital stay are significantly decreased by the latter method. The trap-door approach adds less than 15 minutes to the operating time.

It appears that the breast cancer metastasizes mainly to 2 primary lymphatic systems, the axillary and internal mammary chain. Andreassen and associates,[1] demonstrated in 100 patients who underwent removal of both supraclavicular and parasternal glands that only 3 per cent had involvement of the supraclavicular nodes, whereas the axilla was involved in 41 per cent and internal mammary in 17 per cent. When the axilla was negative no supraclavicular node metastases were found. Wangensteen[24] has found a similar relationship. In his series of 64 patients there were only 4 with supraclavicular involvement when the axillary nodes only were positive, but when both the axillary and internal mammary nodes were positive the number rose to 17 cases.

In medial lesions the internal mammary involvement was found to be 39 per cent in contrast to 17 per cent involvement in the lateral lesions (Table III). Also, when the axillary nodes were positive, the internal mammary node involvement was found to be 3 times as frequent (Table II). For these reasons we have chosen as indications for the internal mammary node dissection medial half and central lesions as well as lateral lesions with clinical evidence of metastases in the axilla.

The removal of the internal mammary nodes has never gained general acceptance because of its technical complexities and difficulties. Handley[6] in his article in 1949 states, "To expose the internal mammary chain is easy; to find lymph glands is difficult because they are often exceedingly small." McDonald and associates,[15] and Haagensen and Stout[3] describe a method of triple biopsy prior to the undertaking of surgery to establish the operability of the patient. They state, "This kind of thorough triple biopsy is obviously not justified in all patients with breast carcinoma. It necessitates an additional separate operative procedure and requires 2 or 3 hours to complete, and it is too much for both patient and surgeon to add this to the very great labor, to use Halsted's phrase, of radical mastectomy as we perform it." We believe that the trap-door technique obviates these objections.

When the trap-door technique is utilized, the bony thoracic cage is anatomically reconstructed. No healing difficulty of the ends of the cartilage has been noted. When a large en bloc excision, such as that utilized by Urban, is carried out, a defect is left on the chest wall which necessitates a fascia lata graft, chest tube drainage, etc. Thus, the problems of postoperative management and morbidity are increased.

SUMMARY

A simplified and practical method of removing the internal mammary nodes during a radical mastectomy is described.

Thirty-four patients with carcinoma of the breast and 1 with malignant melanoma of the chest wall were treated with radical axillary dissection, combined with removal of the internal mammary nodes. In 7 of these cases an en bloc removal of costal cartilage, nodes, and pleura was carried out. In the remaining 28 the "trap-door" approach was used.

Whether the removal of the internal mammary nodes adds to the survival rate of patients with breast carcinoma cannot be ascertained since the follow-up period is too short. One fact which remains quite clear is that the prognosis of patients with involvement of internal mammary nodes is poor.

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HETEROTOPIC BONE FORMATION DEVELOPING IN ABDOMINAL SCARS

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HETEROTOPIC bone formation, or myositis ossificans traumatica, occurring in a cleanly incised and carefully sutured surgical wound seems to be more common than was thought. We have treated 9 of these patients in the past 3 years and one was seen by Dr. H. William Scott of Nashville, Tennessee. In discussing this problem with other surgeons, a surprising number state that they have observed this situation one or more times in their own patients. Sanders[2] found that reports of such cases in the literature were quite rare and stated that he had not personally seen such a case prior to 1943. Whether these are becoming more common in recent years is, of course, impossible to ascertain, but is an interesting subject for speculation.

The symptoms are usually those resulting from the presence of a hard bone in a normally soft structure. Two of these patients (Fig. 1) experienced discomfort from wearing a belt, one had a sticking sensation in his abdominal wall when he bent over to tie his shoes and one asked if we had left a surgical instrument in his abdomen. The bone may be palpated in the depths of the scar and the edges easily outlined. Lateral or oblique x-rays of the abdomen confirm the diagnosis. Calcium can frequently be observed at 2 months (Fig. 2) and fully formed bone found at 6 months. Surgery is routinely advised for those patients who have symptoms arising from these as the progressive nature of this condition makes it unlikely that they will resorb. Three of these cases are asymptomatic and are currently being followed to observe the course their heterotopic bone will pursue.

The 6 cases reported by Sanders and the 10 current ones are summarized in Table I. The condition for which the primary surgery was performed seems to have little bearing on the formation of bone and probably reflects the type of surgery most frequently done by the surgeon. All of these incisions were longitudinal or had a longitudinal component. In Sanders' cases, he comments that these occurred in the upper abdomen only, while in ours two occurred in the lower abdomen. The bone formation in the two lower abdominal incisions were thought to represent recurrent carcinoma and this was the indication for surgery.

The presence or absence of surgical complications seems to have little bearing on the problem since only 2 of the 16 cases had postoperative difficulty. At surgery, the bone is found in the midline fascia or between the anterior fascia and muscle. Dissection disturbs the fascial continuity requiring reapproximation.

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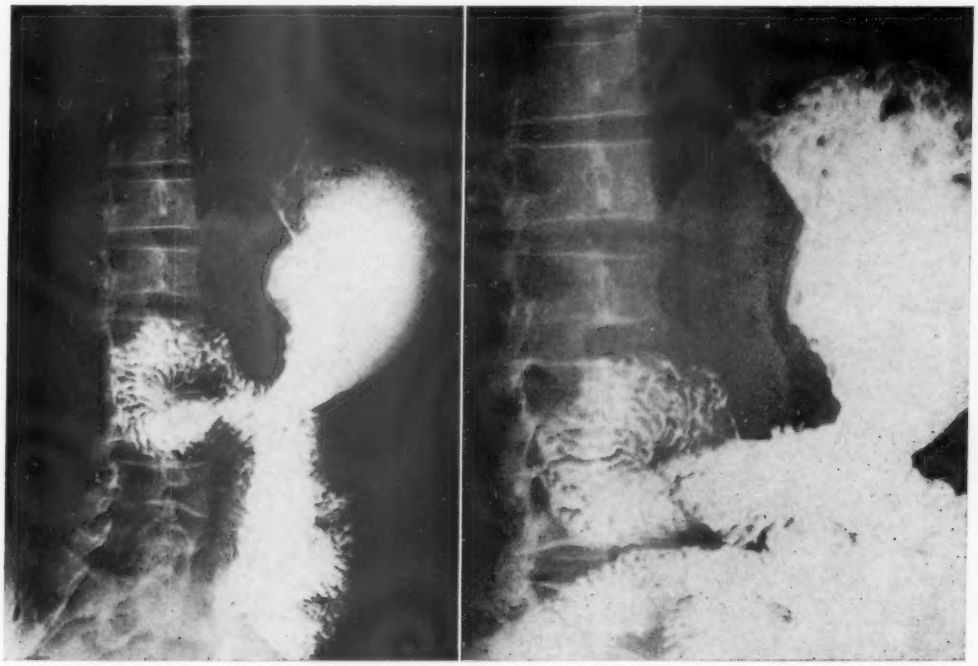
The bones removed from 5 of our patients closely resembled rib (Fig. 3). All of these contained cortical bone and active marrow and 2 had well-defined cartilage which was being replaced by bone (Fig. 4).

Fig. 1.—Patient H. W. Well-developed bone in a midline scar. Notice the transverse fracture through the mid-portion. Prior to this fracture, the patient experienced marked discomfort from wearing a belt. He is now asymptomatic and being observed.



A. *B.*

Fig. 2.—Patient C. W. Note the presence of demonstrable calcium at 2 months and well-formed bone at 1 year.

TABLE I

PATIENT		SANDERS						HM	CW	WF	JH	TT	JG	HH	RS	HW	JD
		JH	LS	LW	AB	AL	FB										
AGE		44	51	49	42	65	61	32	41	61	53	65	65	66	74	50	65
OPERATIONS FOR	Cholecystitis	X					X										
	Duodenal ulcer		X	X				X	X	X	X		X			X	X
	Carcinoma stomach					X						X					
	Hiatal hernia				X												
	Carcinoma sigmoid													X	X		
INCISION	Upper midline	X			X	X		X	X	X	X	X	X			X	X
	Upper paramedian		X														
	Upper pararectus			X			X										
	Lower paramedian													X	X		
COMPLICATIONS	None	X	X	X	X	X		X	X	X		X	X	X	X	X	X
	Duodenal fistula										X						
	Biliary fistula						X										
FIRST NOTED (MO. POSTOPERATION)	Calcium							2	2	2						2	
	Bone	30	11	10	4	7	3	12	12	6	12	16	7	20	8	5	6
LOCATION	Upper	X	X	X	X	X	X	X	X	X	X	X	X			X	
	Middle																X
	Lower													X	X		
X-RAY	Demonstrates	NS	X		X	X	NS	X	X	X	X	X	X			X	ND
	No bone demonstrated													X	X		
LOCATION AT SURGERY	Midline fascia	X	X		RS	X		RS	OB	X	X	X	OB			OB	X
	Between anterior rectus fascia and muscle			X			X							X	X		
	Attached to xiphoid		X								X	X					
	Not attached to xiphoid	X		X		X	X			X				X	X		X
LENGTH (CM.)		8	15	10		11	7	10	8	13	15	10	8	13	4	4	8
PATHOLOGY	Cortical bone	X	X	X		X	NS			X	X	X		X			X
	Active marrow	X	X	X		X				X	X	X		X			X
	Cartilage											X		X			

Patients JG and HW demonstrate attachment of the heterotopic bone to the ensiform process by x-ray but are not so listed here as this has not been shown at surgery.

NS, no statement.
OB, observation.
RS, refused surgery.
ND, not done.

DISCUSSION

The condition of myositis ossificans traumatica occurring in a surgical wound appears to be limited to adult males who have had major abdominal surgery performed through a longitudinal abdominal incision which terminates

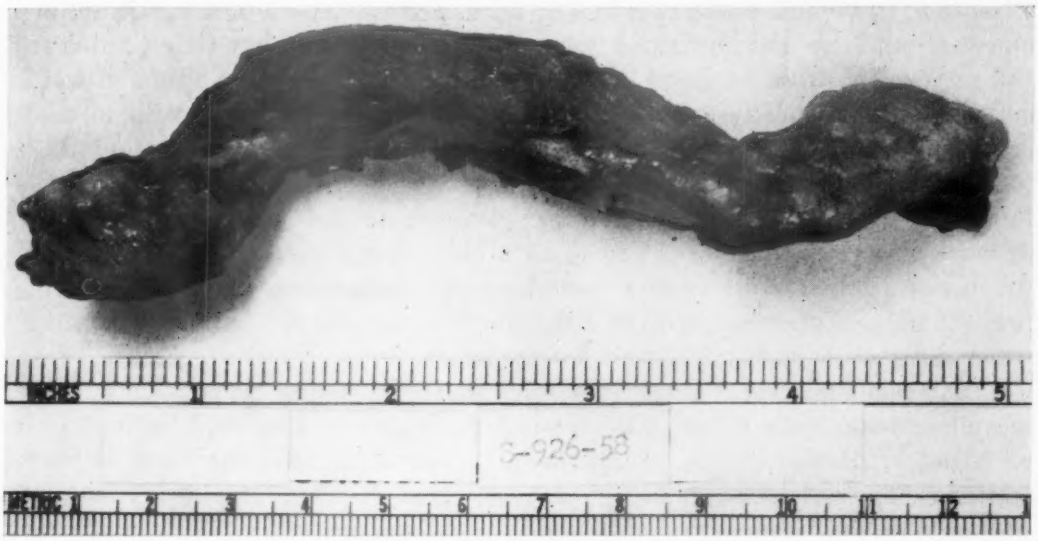


Fig. 3.—Patient W. F. Well-formed bone closely resembling rib.

Fig. 4.—Patient T. T. Cross-section of heterotopic bone showing cortical bone, marrow, and cartilage.

ND, not done.

on a bony or cartilaginous surface. All except one of the surgical specimens reported here closely resembled rib in general appearance; all were true bone and two showed evidence of having formed from cartilage. Five of the 16 were attached to the xiphoid.

Two major theories are currently accepted as explaining heterotopic bone formation. The first states that bits of bone, periosteum, or perichondrium are pulled or cut loose and implanted in the muscle or fascia. Here they proliferate and mature into osseous tissue. The second theory postulates undifferentiated, multipotential connective tissue cells which respond to trauma and its succeeding changes by a process of metaplasia to form new bone. Which one of these theories best explains the formation of these lesions is difficult to say, but the first theory is attractive clinically since all of these incisions ended on a bony or cartilaginous surface, thus providing a good source for bone cells. Each of the bones (except one) closely resembled rib, suggesting implantation from periosteum. Five were attached to the xiphoid and 2 contained cartilage which suggests endochondral bone formation.

Experimental work along this line,[1] however, tends to substantiate the second or metaplastic theory. Heterotopic bone may be produced by traumatic or chemical damage to the musculature, injection of alcoholic bone extracts, intramuscular calcium implants, epithelial transplants to the lower urinary passages, kidney ligation, transplants of gastric mucosa, or ivory pegs imbedded into the muscle. In each of these situations the bone itself is not involved and the opportunity for periosteal cell transplantation therefore is lacking.

Other etiological factors also arise for speculation. Sanders noted that 2 of his patients did physical labor and believed this may have had something to do with the bone formation. All 10 of the present patients are either retired or on a pension and do not do hard work. Calcium determinations were not abnormal in any of the 9 cases in which they were studied. Such conditions as metabolic imbalance states, parathyroid dysfunction, or disturbance in the hydrogen ion concentration were considered. Sophisticated determinations to rule these out were not done but no evidence of such conditions was present clinically.

Inflammation may be incriminated in only the two instances noted although subclinical inflammation, hematoma, and so forth, remain as possibilities. More important is the stress acting on the wound. Longitudinal incisions are subjected to more disruptive force than are transverse ones. None of these bones occurred in transverse incisions nor could any such reported case be found. In the 4 cases in which the Kerr incision was used the bone occurred only in the longitudinal portion.

SUMMARY

The formation of bone in operative scars is apparently not too uncommon and usually requires operative intervention. The mechanism of formation of such lesions is not understood but each of the two currently accepted theories has evidence to support it. In these cases it is certainly possible that both may play a role.

Experimental work on this problem is currently being carried out in the laboratory.

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A GASTRIC HYPOTHERMIA MACHINE

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LOCALIZED gastric hypothermia has recently shown great promise in the control of episodes of massive upper gastrointestinal hemorrhage. It has been effective in a variety of disorders including bleeding from peptic ulcerations, gastritis, and esophageal varices.[3, 4] The alterations in gastric physiology which occur with the employment of gastric cooling and which are felt to play important roles in the arrest of hemorrhage are the marked reductions in gastric digestion, secretion, and blood flow. Control of hematemesis has not been the only function of intragastric cooling. Khalil and MacKeith[2] recommended intragastric cooling for the treatment of hyperpyrexia in children by means of a balloon affixed to the end of a nasogastric tube which was irrigated manually with ice water. Barnard[1] described an intermittent flow type of intragastric cooling machine which he used to produce systemic hypothermia. The present report describes a "closed-system" recirculating hypothermia machine for gastric cooling which provides a constant and equal inflow and outflow and, therefore, a constant intragastric volume.

DESCRIPTION

The apparatus consists essentially of a refrigeration unit, a heat exchanger, and a pump which circulates the cooled solution through a latex balloon inserted into the stomach of the patient. The fluid is introduced into the balloon by the smaller tube of a coaxial plastic tube system and is returned to the machine by the larger tube. The pump of the machine sucks an equal amount of fluid out of the balloon to that introduced into the balloon when the machine is set for recirculation. Unless fluid is added to the balloon from the reservoir or taken from the balloon into the reservoir, the circulating volume of fluid within the system remains constant. All fluid transfer to or from the gastric balloon is reflected directly by the fluid level in the reservoir (Fig. 1, *F*).

The gastric balloon (Fig. 1, *A*) is attached to the end of a coaxial tube system (Fig. 1, *B*) which consists of an outer clear No. 18 Fr. polyvinyl tube and an inner PE 260 polyethylene tube. These in turn are connected by a "Y" adapter to 2 clear polyvinyl tubes which attach to the pumping system by threaded couplers (Fig. 1, *C*) at the side of the machine. The outside diameter of the tube assembly (No. 18 Fr.) allows passage through the nose which is more easily tolerated than peroral passage.

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Filling and emptying of the gastric balloon are controlled by 2 fluid circuit switches (Fig. 1, *D*) which direct fluid to, from, or around the reservoir depending upon the function selected. There are 3 positions that may be selected,

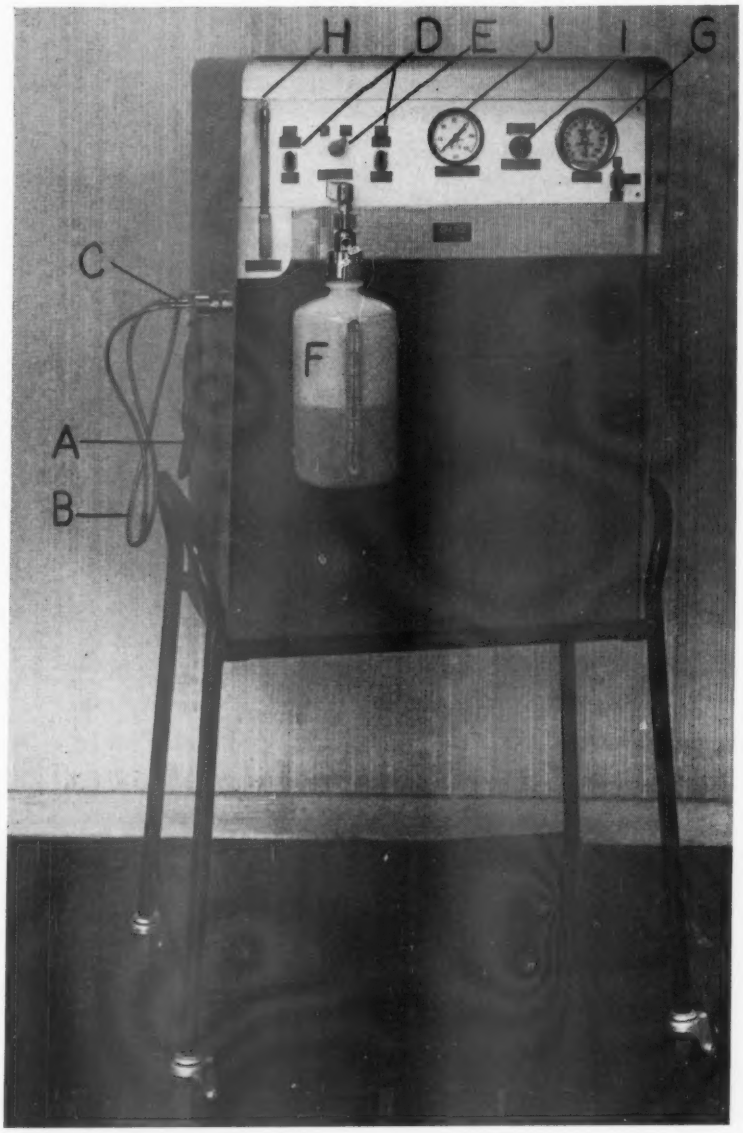

Fig. 1.—*A*, Gastric balloon. *B*, Coaxial tube assembly (outer No. 18 Fr. polyvinyl, inner PE 260). *C*, Threaded couplers. *D*, Fluid circuit switches. *E*, Air bleed valve. *F*, Reservoir. *G*, Inflow thermometer. *H*, Outflow thermometer. *I*, Fluid temperature control. *J*, Pressure gauge.

"fill," "run," and "empty." Any trapped air in the fluid system is eliminated through an air bleed valve (Fig. 1, *E*) located at the top of the fluid system. The reservoir (Fig. 1, *F*) is placed on the outside of the machine so that a visual indication of the amount of fluid that has been put into the gastric balloon is always at hand.

The temperature of the circulating fluid is governed by an electrothermostatic control (Fig. 1, *I*). The temperatures of the fluid entering and returning from the gastric balloon are indicated by thermometers (Fig. 1, *G*, *H*). Dual thermometers give an indication of the heat gain of the fluid in the stomach during circulation and also the actual temperature of the stomach fluid. In practice the temperatures used have been in the range of 0° to –5° C. in order to maintain a stomach wall temperature of 10° to 14° C.

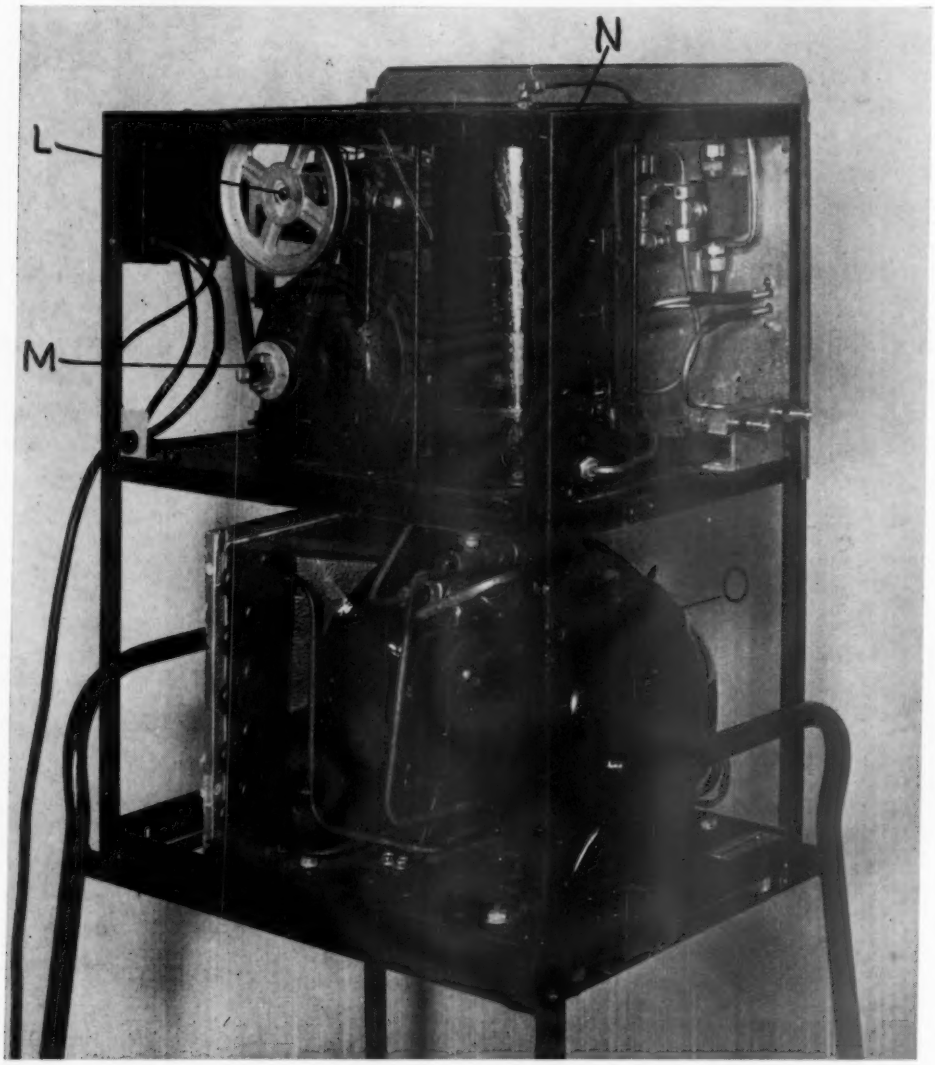

Fig. 2.—*L*, Gear type pump, rated capacity 0.46 gal. per minute against 60 pounds per square inch. *M*, ¼ H.P. motor, 1,725 r.p.m. split phase. *N*, Heat exchanger. *O*, Condensing unit, 3,100 B.T.U. per hour.

Pressure and circulation are provided by a gear type pump (Fig. 2, *L*) which recirculates approximately 750 c.c. of fluid per minute at 0° C. and maintains a 3° temperature difference between the inflow and outflow tubes. The pressure of the pumping system is indicated by a gauge (Fig. 1, *J*) which is controlled by a fixed pressure regulator located behind the front panel. If a

rise in pressure in the system occurs the pressure regulator automatically shuts off the pumping mechanism. Power is provided to the pump by a ¼ H.P. motor. During recirculation fluid from the gastric balloon is received by the pump and is delivered to the heat exchanger (Fig. 2, *N*) where it is cooled down to the selected temperature by the condensing unit (Fig. 2, *O*). From the heat exchanger the fluid is forced through the inner tube of the coaxial assembly and into the gastric balloon. From the balloon the fluid is forcibly returned to the machine through the outer tube to complete the cycle. Fig. 3 is a schematic diagram of the machine and its components.

The solution used in the system contains two-thirds water and one-third ethyl alcohol in order that temperatures below the freezing point of water may be attained. If water alone is used, 4° C. is the lowest temperature that can be reached.

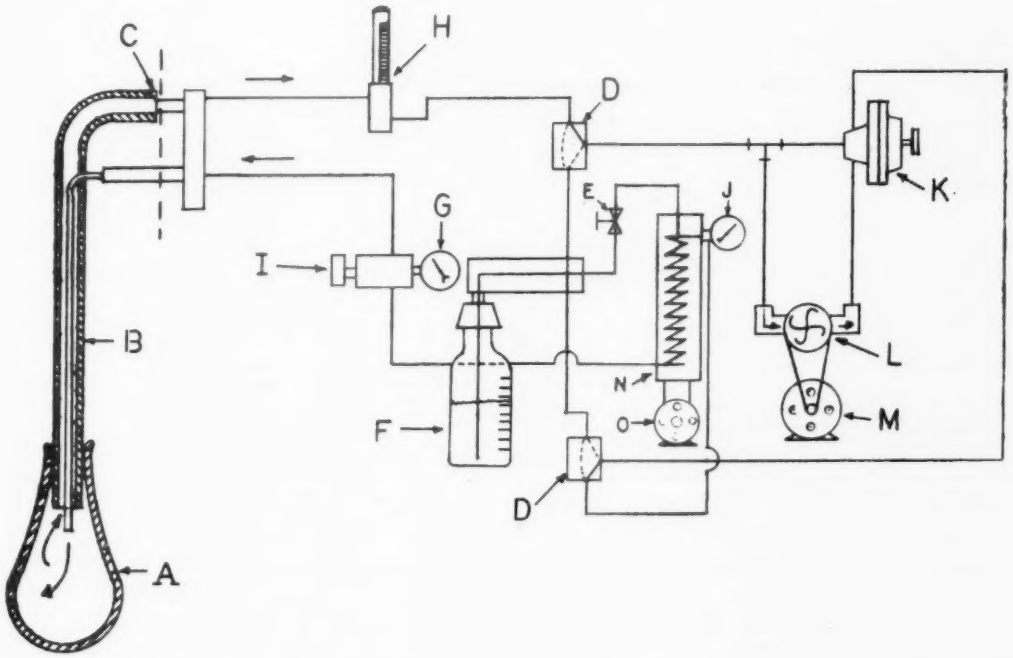

Fig. 3.—*A*, Gastric balloon. *B*, Coaxial tube assembly (outer No. 18 Fr. polyvinyl, inner PE 260). *C*, Threaded couplers. *D*, Fluid circuit switches. *E*, Air bleed valve. *F*, Reservoir. *G*, Inflow thermometer. *H*, Outflow thermometer. *I*, Fluid temperature control. *J*, Pressure gauge. *K*, Pressure regulator valve. *L*, Gear type pump, rated capacity 0.46 gal. per minute against 60 pounds per square inch. *M*, ¼ H.P. motor, 1,725 r.p.m. split phase. *N*, Heat exchanger. *O*, Condensing unit, 3,100 B.T.U. per hour.

METHOD OF OPERATION

The patient is given a sedative and placed in the semi-Fowler's position. A large-bore nasogastric tube is inserted into the stomach to lavage the stomach of all blood and clots. This is left in place and attached to suction so that further bleeding or cessation of bleeding can be noted. Whole blood is given as needed to restore the blood volume.

The nasopharynx is sprayed with a topical anesthetic solution. The gastric balloon and coaxial tube assembly are lubricated and inserted through the nose

and into the stomach. The machine is turned on, and the switches on the control panel are placed in the "fill" position. When the selected amount of fluid (750 to 1,000 c.c.) has been observed to have run out of the reservoir (and hence into the balloon), the switches are changed to "run." This keeps the circulating volume constant. When hemorrhage has stopped, as judged by the absence of bloody returns in the suction bottle, the clinical status of the patient, the physical signs, and the hematocrit, the balloon is emptied by setting the switches to "empty." When the gastric balloon is empty as noted by the return of the fluid in the reservoir to the prefilling level, the machine is shut off and the balloon is withdrawn.

During the employment of gastric hypothermia body temperature is maintained by a heating blanket since systemic hypothermia is produced without external heating. Body temperature is monitored by an intrarectal thermometer.

SUMMARY

A "closed system" recirculating gastric hypothermia machine for use in treating massive upper gastrointestinal hemorrhage has been described.

This study was made possible through the cooperation of the O. E. M. Corporation in East Norwalk, Connecticut. The apparatus is currently in production at the O. E. M. Corporation.

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SEVERE HYPERTONICITY OF THE EXTRACELLULAR FLUID ASSOCIATED WITH CEREBRAL LESIONS

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THE role and significance of volume receptors and osmoreceptors in maintaining normal concentrations of extracellular electrolytes has not yet been clarified. Some indirect evidence for the presence of "osmoreceptors" in that portion of the dog's brain normally supplied by the internal carotid arteries has been presented by Verney.[9]

Normal mechanisms for sustaining the tonicity of the extracellular fluid involve an interaction between many organs and hormones. The degree of hypertonicity of the extracellular fluid observed in the cases reported here has been detected only in individuals with known cerebral lesions. Cooper and Crevier[3] have hypothesized that the extreme alterations in fluid and electrolyte balance which occur with cerebral lesions might be caused by some defect in the osmoreceptor mechanism. This study offers further evidence for the cerebral origin of these abnormalities and interrelates some metabolic data with specific clinical problems.

CASE REPORTS

CASE 1.—S. W., a 9-year-old girl, was admitted with a history of headaches of 3 to 4 years' duration. The headaches, which were primarily frontal, became progressively more severe 1 month preceding hospitalization. One week before admission she fainted twice. The day prior to admission her mother noticed that she staggered when walking. A recent history of falling asleep in school was obtained. Past medical history was noncontributory. The child had had measles, mumps, and chicken pox without sequelae. Urinary urgency was also present.

Physical examination revealed a thin, listless girl who cried out several times because of headache. She was physically underdeveloped for her age. Vital signs were normal. There was no gross limitation of motion in the extremities or any abnormal movements. Cooperation could not be obtained for muscle testing. Pain perception was intact. Pupils were regular and equal and reacted to light and accommodation. Extraocular movements were normal. A temporal defect in the visual field was present on the right. Fingers could be counted at 5 feet. Funduscopic examination of the left eye was normal, while in the right eye the margins of the disc were blurred and elevated 1 to 2 diopters. Cranial nerves V and VII through XII were intact. Reflexes were normal except for bilateral extensor plantar responses.

Erosion of the sella turcica with suprasellar calcification was seen in roentgenograms of the skull. The hemoglobin concentration was 13.0 Gm. per cent and the white blood cell count was 7,100 per cubic millimeter. The urine was normal, and specific gravity was 1.015.

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The clinical impression was that of a craniopharyngioma. Following preoperative cortisone administration, a ventriculogram was performed. The intraventricular pressure was greater than 600 mm. of water. X-rays showed dilated lateral ventricles with nonfilling of the third ventricle. A tumor in the region of the anterior portion of the third ventricle was subtotally removed the same day. No normal pituitary gland was identified. At the conclusion of the craniotomy, a tracheostomy was performed. Histologically the tumor was a craniopharyngioma.

Postoperatively, oral intake and output appeared adequate. The patient moved all 4 extremities and responded slowly to spoken commands. By the fifth postoperative day she no longer responded to verbal orders, and purposeless movements of all extremities occurred periodically. On the twelfth postoperative day her lethargy increased, and, for the first time, a nonlateralizing convulsive seizure occurred. The convulsive episode seemed to be caused by water intoxication. On the sixth postoperative day a hypernatremia and a hyperchloremia were present (Fig. 1). On the eighth postoperative day the serum chloride had increased to 129 mEq. per liter. It was then noted that the specific gravity of the urine postoperatively had been persistently less than 1.010. A presumptive diagnosis of diabetes insipidus was made. On both the tenth and the eleventh postoperative days, 2.5 mEq. per liter of Pitressin Tannate in Oil were given. The urinary output decreased sharply during the subsequent 72 hours. Concomitantly, the serum sodium fell by 28 mEq./L. and the serum chloride by 19 mEq./L. On the thirteenth postoperative day 2 more convulsive seizures occurred. Determinations of the serum electrolytes demonstrated that the sodium had fallen to 112 mEq./L. and the chloride to 81 mEq./L. Serum potassium was 3.3 mEq./L. Three per cent NaCl and 0.2 mg. 9-alpha-flurohydrocortisone were then given. On the fourteenth postoperative day the child was clinically improved and the serum electrolytes were within normal limits except for the chloride which was 113 mEq./L. Electrolyte determinations on the seventeenth postoperative day again revealed a hypernatremia and hyperchloremia. In retrospect it was noted that the patient had been in negative water balance during the previous 4 days. Pitressin Tannate in Oil (2.0 U.) was then given and the urinary output decreased while the serum concentrations of sodium and chloride also fell. On the nineteenth postoperative day, because of the return of the serum sodium to 177 mEq./L. and the serum chloride to 128 mEq./L., Pitressin Tannate in Oil (2.0 mEq. per liter) was given again. The urinary output decreased markedly and the serum electrolytes returned to normal levels. Each time the electrolytes approached normal ranges, the patient became more alert and responded to commands. When she received an oral diet, but no Pitressin, the serum sodium stabilized at about 165 mEq./L. and the serum chloride at about 121 mEq./L. From the twenty-third postoperative day until the time of discharge, on the seventieth postoperative day, the patient's condition did not change appreciably. Metabolic balance studies were obtained between the nineteenth and the thirty-first postoperative days (Fig. 1).

At the time of discharge, the child was semicomatose, responding only to painful stimuli. She would occasionally cry without obvious cause but did not speak. Spontaneous movements of the extremities occurred rarely. She was discharged with the recommendation that she receive 1 U. of Pitressin weekly. Feedings at home consisted of a formula given through a nasogastric tube.

The patient had 4 subsequent admissions to the hospital. The second admission, 4 days following the initial discharge, was for bilateral bronchopneumonia. She was treated with antibiotics and was improved by the time of discharge. No electrolyte determinations were obtained on this occasion. Her third admission was 4 months postoperatively. She was hospitalized for 5 days to correct a dietary problem. At that time the serum sodium was 141 mEq./L., potassium 4.1 mEq./L., chloride 105 mEq./L., and bicarbonate 26 mEq./L. On the fourth admission, 5 months postoperatively, the patient was comatose and unresponsive. She had suddenly collapsed 24 hours previously. Serum sodium was 218 mEq./L., chloride 140 mEq./L., potassium 3.2 mEq./L., bicarbonate 27 mEq./L., and the blood urea nitrogen 15 mg. per cent. The rectal temperature was 104° F. A urinary tract infection was present. She responded to supportive treatment with hydration and Pitressin, and

was improved upon discharge 18 days later. Right upper lobe pneumonitis necessitated the fifth admission approximately 7 months postoperatively. Serum electrolytes then were sodium 147 mEq./L., chloride 116 mEq./L., potassium 3.7 mEq./L., bicarbonate 24 mEq./L., fasting blood sugar 83 mg. per cent, and blood urea nitrogen 20 mg. per cent. She was discharged from the hospital 3 days later and has not returned since.

CASE 2.—R. B., a 50-year-old physician, was in good health, except for occasional left frontal headaches, until 2 days prior to admission when he fell suddenly to the ground and shortly thereafter lost consciousness. Subsequently, he regained consciousness but complained of severe headaches. Lumbar puncture revealed grossly bloody spinal fluid under increased pressure. The patient again became comatose and was transferred to University Hospital.

On admission the blood pressure was 155/75 mm. Hg, pulse 75 per minute, respirations 20 per minute, and the rectal temperature 99° F. The remainder of the general physical examination was negative. He responded only to deep stimulation. Marked nuchal rigidity and positive straight leg raising signs were present. Subhyaloid and retinal hemorrhages were seen. The margins of the discs were sharp. Visual acuity tests were not possible. The eyes deviated to the right and the pupils were miotic. A right lower facial palsy was demonstrable. Motor examination showed increased muscle tone on the right. An extensor plantar response was present on the right and equivocal on the left. The hemoglobin was 11.6 Gm. per cent and the urinalysis was negative. Specific gravity of the urine was 1.024.

The level of consciousness deepened during the 24 hours following admission. Bilateral carotid arteriograms showed an aneurysm of the anterior communicating artery at the junction with the right anterior cerebral artery. A right frontal craniotomy was immediately performed and a large aneurysm visualized. Multiple clips were placed in the dome of the aneurysm and at its neck. The patient tolerated the procedure well, but postoperatively he did not regain consciousness. On the sixth postoperative day (November 4) the operative wound was re-explored but no significant hematoma or softening of the frontal lobe was found. The patient's coma was attributed to hypothalamic and deep frontal lobe injury resulting from the previous aneurysmal hemorrhage. Postoperatively, vital signs remained stable, but the clinical condition did not improve. On November 6, the serum sodium was 163 mEq./L., chloride 125 mEq./L., potassium 4.1 mEq./L., bicarbonate 28 mEq./L., and blood urea nitrogen 66 mg. per cent (Fig. 2). Although the values of the serum electrolytes had been normal prior to the first operation, 2 days later a hyperchloremia of 106 mEq./L. was present. On the fifth postoperative day a hypernatremia of 154 mEq./L. associated with a further increase of the serum chloride of 112 mEq./L. was noted. Blood urea nitrogen was 29 mg. per cent. The patient had been given cortisone prior to the first operation, and received 150 mg. daily until 12 days following the second operation. The cortisone dosages were then progressively decreased and finally stopped 2 days prior to discharge from the hospital. On November 7, serum sodium had increased to 172 mEq./L. and the chloride remained at 125 mEq./L. The patient continued to be comatose and unresponsive. A review of the 24 hour fluid intake and output since the first operation showed that although 24 hour urinary volume outputs between 920 c.c. and 2,575 c.c. were excreted, the patient had been in negative water balance. Positive water balance was then achieved by the administration of increased fluid volumes by a nasogastric feeding tube. Balance studies were conducted during this period of hydration (Fig. 2). The nasogastric feeding tube was used to minimize the danger of cerebral edema which could follow the rapid administration of intravenous fluids. When positive water balance was established, the serum electrolytes returned toward more normal values. On November 15, the serum sodium was 152 mEq./L., chloride 115 mEq./L., potassium 4.3 mEq./L., and the blood urea nitrogen 26 mg. per cent. The patient's clinical condition improved concomitant with this improvement in the serum electrolytes. On November 11, he was oriented as to time and place, and able to respond to verbal commands. Beginning on November 15 the daily cortisone dosages were progressively reduced until November 25,

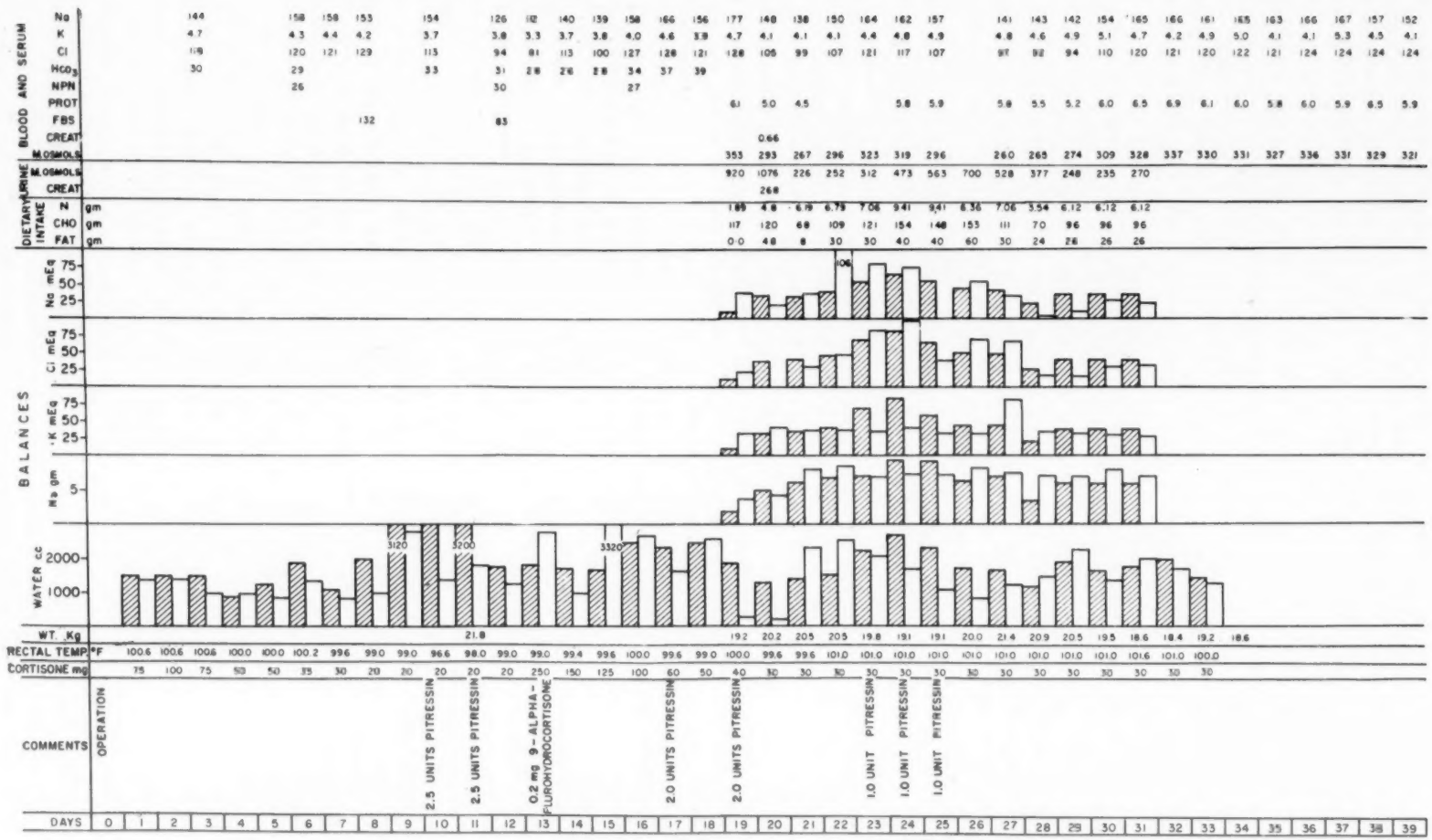

Fig. 1.—Case 1. Black columns indicate intake and white columns urinary output. Nitrogen is total nitrogen excreted. Bicarbonate and electrolytes are expressed in milliequivalents per liter. Serum creatinine, nonprotein nitrogen, and fasting blood sugar (FBS) are expressed in milligrams per cent; milliosmols as per 1,000 Gm. of water; and protein as grams per 100 c.c. Urine creatinine is milligrams excreted per 24 hours. Temperature is mean rectal.

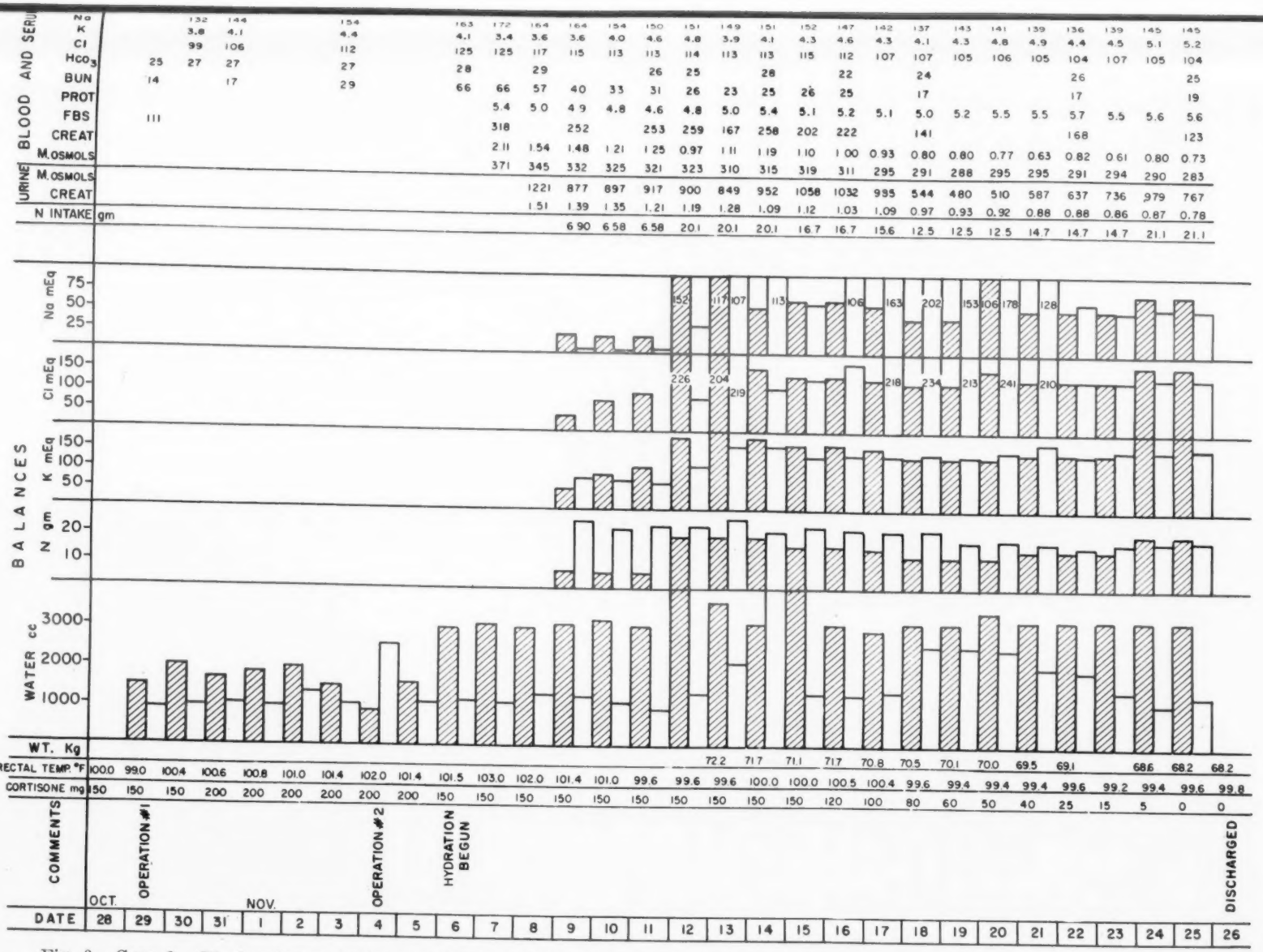

Fig. 2.—Case 2. Black columns indicate intake and white columns urinary plus stool output. Nitrogen is total nitrogen excreted. Bicarbonate and electrolytes are expressed in milliequivalents per liter. Blood urea nitrogen, fasting blood sugar (FBS), and serum creatinine are expressed in milligrams per cent; milliosmols as per 1,000 Gm. of water; and protein as grams per 100 c.c. Urine creatinine is grams excreted per 24 hours. Temperature is mean rectal.

when he received none. The decrease in cortisone dosage and continued hydration was associated with a further reduction in the concentrations of the serum electrolytes. Normal levels of these ions were present by November 25.

Upon discharge, his speech was clear. He was readmitted to the hospital for physiotherapy on January 30. Since his previous hospitalization he had been eating and drinking fluids ad libitum. Serum electrolytes on this admission were normal, sodium 142 mEq./L., potassium 4.1 mEq./L., chloride 105 mEq./L., and proteins 6.2 Gm. per cent.

DISCUSSION

These 2 cases represent examples of hypertonicity of the extracellular fluid developing secondary to depletion of body water. This condition is uncommon in the absence of cerebral lesions because highly developed physiologic mechanisms mediated through the central nervous system, thirst and antidiuresis, normally compensate for this unusual situation.

Restriction of water in normal individuals does not result in significant increases in the tonicity of the extracellular fluid. Even in the early stages of water depletion the subject complains bitterly of thirst. Since water is then supplied, either orally or parenterally, further dehydration is prevented. Although Nadal and associates[6] withheld all fluids from a normal subject for 4 days, the extracellular electrolytes did not become hypertonic. However, thirst became marked. The thirst mechanism is presumably actuated by losses of intracellular and extracellular fluid and not by the degree of hypertonicity of the extracellular fluid per se.[8] The regulation of the tonicity of the extracellular fluid, in the early stages of water depletion, is dependent upon 2 physiologic processes, (1) renal excretion of sodium and chloride ions equivalent to the deficit of body water, and (2) maximal water reabsorption. As water deprivation continues, the kidneys, presumably under the influence of antidiuretic hormone, continue to reabsorb water. In addition, sodium and chloride ions are reabsorbed and the urine is concentrated maximally in a compensatory attempt to prevent further depletion of the volume of extracellular fluid. Since obligatory water losses continue in the absence of an adequate intake of water and since reabsorption of sodium and chloride ions is maximal under these circumstances, the extracellular fluid becomes hypertonic. The comatose patient, unable to express thirst, may progress to the late stages of dehydration before the disproportion between fluid intake and output is recognized. Furthermore, in situations where obligatory losses of water are increased, as in diabetes insipidus or in instances of increased protein catabolism, hyperosmolality of the extracellular fluid will develop more rapidly.

Conceivably, hypertonicity of the extracellular fluid may also occur in situations in which there is interference with the function of the "osmoregulatory" mechanism. If osmoreceptors do exist in humans, they should respond to small degrees of change in the osmolal concentration of the extracellular electrolytes. Verney[9] believes that an increase in tonicity of the extracellular fluid is normally prevented by an osmoregulatory response to small increases in concentration of extracellular electrolytes. This osmoregulatory response may be manifested as either an increased renal excretion of sodium and chloride ions or an inhibition of urine flow, or both. If a defect in osmoregulatory

function exists, then relatively small deficits of body water could lead to hypertonicity of the extracellular fluid, since compensatory urinary losses of sodium and chloride would not occur or because the normal antidiuretic response would not take place. Again, situations which would increase obligatory water losses would tend to cause the more rapid development of the hypertonic state unless adequate supplies of exogenous water were made available. It is possible, then, that the severe degree of hypertonicity which is observed in some patients with cerebral lesions is related to a disturbance of an osmoregulatory system which is operative in individuals without cerebral disorders. In this manner, extreme increases in the concentration of the extracellular electrolytes may be associated with relatively small deficits of body water. The classic studies of Verney, indicating the presence of receptors in the central nervous system of the dog which respond to increases in osmotic pressure of the cerebral blood by inhibiting urine flow, have not been repeated in humans. It is likely that such osmoreceptors do exist in the human brain and that the hypertonicity of the extracellular fluid observed in some patients with cerebral lesions is related to interference with their function.

In Case 2 of this report, inhibition of urine flow occurred only after the extracellular fluid became markedly hypertonic. Although this patient's kidneys were able to concentrate urine to 1,221 milliosmols per liter when the serum osmolality was 345 milliosmols per liter, a relatively normal urinary osmolality was present when the extracellular fluid was less hypertonic (Fig. 2). These data suggest that, although osmoregulatory activity is present, as manifested by antidiuresis, a greater degree of hypertonicity of the extracellular fluid is required to produce an antidiuretic response in this patient than in a normal patient.

Cooper and Crevier[3] have stated that there was no evidence of an insufficient intake of fluid or loss of excessive water in their patients. In each of the 2 cases they reported, the daily urinary output varied between 600 and 1,600 ml., but no mention was made of exact intakes of fluid in relation to urinary volumes. A 24 hour urinary output of 1,600 ml. does not indicate a satisfactory degree of hydration unless renal function is known to be normal and unless the degree to which the kidneys must concentrate the urine to excrete this volume is also known. For example, in Case 2, the 24 hour urinary volume of 1,330 ml. excreted on November 8 was concentrated to 1,221 milliosmols per liter, which approached the maximal concentrating power of the normal kidneys. This finding would indicate that this patient's kidneys were reabsorbing water in a normal fashion. The excretion of such a concentrated urine is suggestive of a significant degree of dehydration while the large urinary volume represents the minimal amount of urine into which the kidneys can excrete the contained solute load. Therefore, excretion of a large volume of urine of high osmolality is not evidence of adequate body hydration but merely represents obligatory losses of fluid. Cooper and Crevier further mentioned that there was no clinical evidence of dehydration in their reported cases. There were no clinical manifestations of dehydration in the 2 cases reported here either. However, in Case 2, the fact that dehydration

was present is substantiated by the high osmolality of the 24 hour specimens of urine even after positive water balance had been established (Fig. 2). The lack of clinical signs of dehydration in patients with cerebral lesions and hypertonic extracellular fluid may be explained on the basis that only moderate losses of body fluid have been sustained in those instances in which the osmoregulatory system is malfunctioning. It is not proposed that this interpretation is incontrovertible. It is, however, compatible with the facts available.

In cases which we have observed, serum electrolytes have returned to normal concentrations when a positive water balance has been re-established. This phenomenon has been previously noted by Wolfman and Schoch[10] and

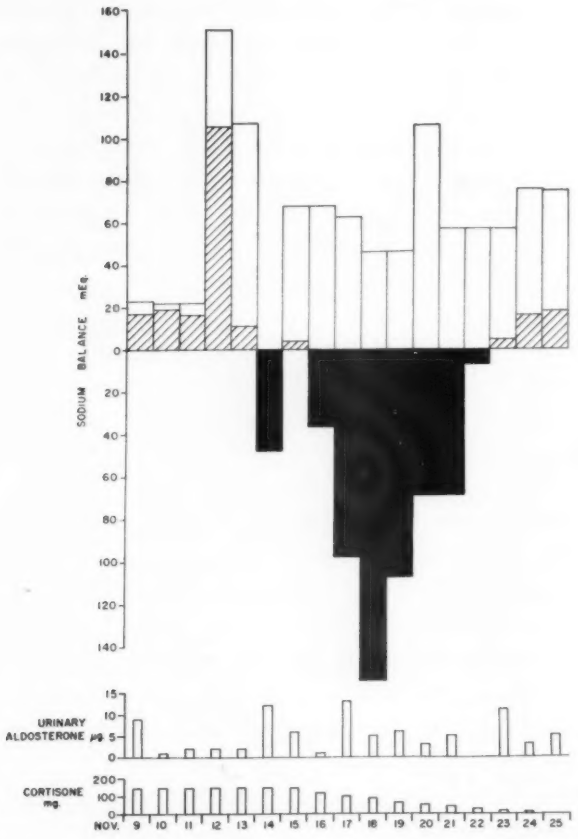

Fig. 3.—Case 2. Sodium balance during period of study. Negative sodium balances are associated with a decrease in the cortisone dosages.

Gordon and Goldner.[4] Wolfman and colleagues[11] have noted 2 patients with cerebral lesions who manifested hypernatremia, hyperchloremia, hypokalemia, and azotemia. Respective deficits in the total blood volume of 55 per cent and 61 per cent of that expected would suggest that a significant degree of dehydration was present in these cases also.

Hyperfunction of the adrenal cortex seldom produces hypernatremia greater than 150 mEq./L.[1, 7] Even in cases of primary aldosteronism, the serum sodium seldom exceeds 150 mEq./L. August and associates[2] have administered large amounts of aldosterone to normal subjects and found that after an initial

period of weight gain accompanied by retention of sodium, the gain in weight ceased, and the excretion of sodium returned to control levels despite the continued administration of this hormone. Hypernatremia did not occur. One would, therefore, be reluctant to indict the exogenous administration of cortisone as a causative agent in the production of the hypernatremia and hyperchloremia in the cases here reported. Nevertheless, the findings in Case 2 suggest that patients with certain cerebral lesions may be more sensitive to the administration of this hormone than normal persons. Fig. 3 depicts the sodium balance of the Case 2 patient during the period of metabolic balance. It was possible to reduce the hypernatremia and hyperchloremia by the simultaneous administration of sodium and chloride ions, calories, and water. The maximum benefit from this regimen was achieved in 72 hours, and no further clinical or chemical improvement occurred until the dosages of cortisone were

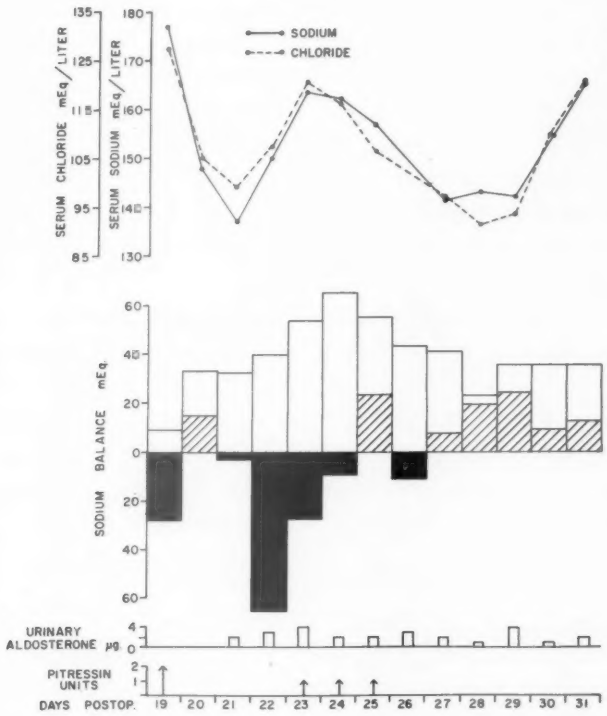

Fig. 4.—Case 1. Correlation of serum sodium and chloride levels with sodium balance when Pitressin was given. Urinary aldosterone excretions are within the normal range or low.

decreased. Except for November 14, the sodium balance was persistently positive during the daily administration of 150 mg. of cortisone. With the reduction of the cortisone dosage on November 16, there was an increase in the urinary excretion of sodium accompanied by increased excretions of chloride and water. At the conclusion of this diuresis the serum electrolyte was normal and remained so. Interestingly, the urinary excretion of aldosterone was never greater than normal.*

*The urinary aldosterone assays were performed by the Bio-Science Laboratories, Los Angeles, Calif.

Case 1 demonstrates an interesting and previously unreported phenomenon. On the nineteenth postoperative day, the serum sodium was 177 mEq./L. and the chloride 128 mEq./L. The administration of 2 U. of Pitressin Tannate in Oil was followed by antidiuresis for 48 hours, increased urinary osmolality, and decreased concentrations of serum electrolytes (Fig. 4). Simultaneously, a change toward a more positive sodium balance occurred. This change represents increased reabsorption of sodium by the kidneys, preventing a precipitous fall of this ion to abnormal levels. As the effect of Pitressin diminished, negative balances of sodium again developed. The urinary excretion of aldosterone during the period of administration of Pitressin did not correlate with the fluctuations in sodium balance. The levels of urinary aldosterone were never increased. Changes from negative to positive sodium balance in this patient appear to be related more to an expansion of extracellular fluid volume than to increased production of aldosterone. Leaf and colleagues[5] administered Pitressin Tannate in Oil to persons receiving a large oral intake of water. They noted that the expansion of total body water which occurred was accompanied by an increase in body weight, a decrease in serum sodium concentration, a decrease in the urinary excretion of aldosterone, and increased renal excretion of sodium. In Case 1, the renal excretions of sodium did not increase, and the excretions of urinary aldosterone showed no appreciable change with administration of Pitressin. Possibly, in the presence of impaired cerebral osmoregulatory function, this patient's responses were mediated essentially by volume changes.

Evidence that the metabolic abnormalities detected in certain patients with cerebral lesions might be only of a temporary nature can be gleaned from the subsequent clinical course of the patient described in Case 2. This patient returned to the hospital for physiotherapy 65 days after discharge. On that occasion the serum electrolytes were normal. This would indicate that, in certain instances, early detection and appropriate therapy of these metabolic abnormalities can result in their complete correction.

SUMMARY

Metabolic studies on 2 patients with severe hypertonicity of the extracellular fluid are presented. Both had cerebral lesions. Possible mechanisms for the development of this abnormality are discussed.

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AUTOTRANSPLANTATION OF LIVER: DESCRIPTION OF A METHOD

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AUTOTRANSPLANTATION of the mammalian liver has been attempted and performed many times. Cameron[1] credits Alessandri (1895-1897) with being the first to transplant living liver. Since then other investigators have transplanted liver to various sites including the camera anterior chamber, subcutaneous region, and peritoneum.[1, 2, 3] The features which have been characteristic of most of these endeavors are: (1) the free grafting of small fragments or slices of liver tissue, (2) the survival of only the most peripherally placed hepatic cells in such grafts, (3) the proliferation of bile canaliculi, and (4) the seeming dissociation between the remaining hepatic cells and the bile ducts.[1, 2] When revascularization has been attempted as a gradual or staged procedure, the results have been improved, but many of the characteristics of the former grafts have been retained.[4, 5]

The purpose of this report is to present a method of autotransplanting a relatively large quantity of canine liver. Preliminary results appear to indicate that a high degree of hepatic cell viability can be achieved with this technique.

METHOD

Healthy, adult, mongrel dogs of both sexes weighing between 9 and 20 kilograms were used. Prior to entering the experiment, all animals were quarantined for 2 weeks and immunized against distemper and hepatitis.

Transplantation was accomplished by a two-stage operation with a 3 to 4 month interval. Procaine penicillin (600,000 units) was administered 1 or 2 days before and for 1 week after each operation. Intravenous pentobarbital sodium anesthesia and tracheal intubation was employed in all instances. Blood transfusions (100 to 200 ml.) were used during most of the operations.

First Stage.—Through a midline laparotomy incision the small intestine was transected about 30 cm. distal to the location of the pancreas in the duodenal mesentery. Anastomosis (end to side) of the proximal end of small bowel to the distal loop of small bowel was performed in the manner of Roux. The free loop of the "Y" thus created was 40 to 45 cm. in length. This free limb was incised along its antimesenteric border for a distance of 12 to 14 cm., as measured from the open end. The exposed mucosa was next excised by means of a plane developed deep to the muscular layer, and a denuded seromuscular flap, with its blood supply intact, was thereby created. The open end of the free limb

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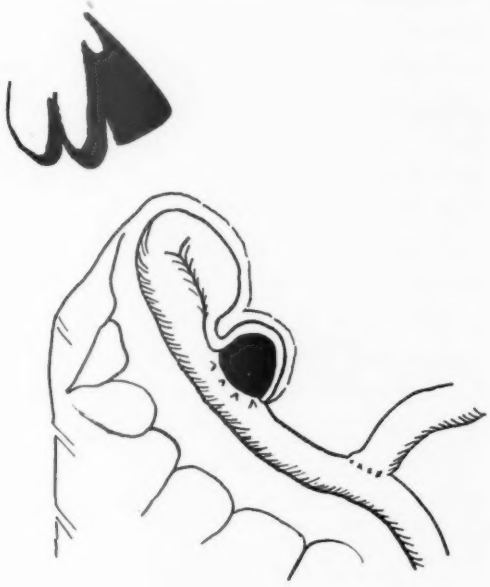
of the "Y" was closed in 2 layers. A liver lobe was then selected to serve as the transplant. Selection of this lobe was based on its proximity to the upper aspect of the midline incision and its narrowness of width (a small diameter lobe would be easier to anastomose later to the bowel). The raw surface of the seromuscular flap was attached with interrupted No. 4-0 silk sutures to the peripheral pole of the hepatic lobe. This "enterohepatopexy" was constructed in a manner which would permit the seromuscular flap to envelop the liver lobe on its 2 broad surfaces. The liver was gently scarified before it was covered by the denuded surface of the enteric flap. The completed first stage operation is depicted in Fig. 1.

Second Stage.—Three to 4 months after the first, the second stage operation was performed. A midline laparotomy incision was made and the previously fashioned "enterohepatopexy" was located. The tip of the liver lobe, to which the enteric flap was now well adherent, was amputated. Hemostasis of the cut

First Stage

Fig. 1.



Second Stage

Fig. 2.

Fig. 1.—The Roux "Y" is constructed. The enteric flap, fashioned from the end of the free limb of the "Y," is sutured to the liver.

Fig. 2.—The transplant is severed from the parent liver lobe and anastomosed into an opening in the side of the free limb of the Roux "Y."

edge of the parent lobe was attained by mattress sutures of No. 2-0 silk often supplemented by tamponade with cellulose sponge. An opening was made in the side of the free limb of the Roux "Y," 3 to 4 cm. proximal to the closed end of the limb. The liver transplant, which measured 3 to 5 cm. in greatest diameter, was manipulated in a manner which allowed its freshly cut surface to occupy the opening in the side of the bowel. In this position a 2 layer anastomosis was performed between the liver transplant and the limb of the Roux "Y." The inner layer of the anastomosis consisted of a continuous inverting

No. 3-0 chromic catgut suture, and the outside layer of interrupted No. 4-0 silk Lembert sutures. The cut edge of the graft could now discharge its secretions into the small bowel. The complete second stage operation is presented in Fig. 2.

DISCUSSION

In order to improve the survival of hepatic cells in the autografts, an attempt has been made to establish the new blood supply before severing the old. This is an established principle in plastic surgery and has been used before in liver transplantation.[4, 5] Provision for egress of the biliary secretion of the transplant is also important. If the transplanted liver is to behave as a coordinated unit functioning like the parent organ, bile must be allowed to drain. The described method permits the bile not only to drain from the transplant, but also to enter the intestinal lumen.

Two major complications were encountered in the preparation of the autotransplants. The first was autolysis of the liver lobe to which the enteric flap was sutured. This resulted in the death of 5 consecutive animals until the policy of antibiotic adjuvant therapy was instituted. The second obstacle to successful construction of the preparations was leakage at the anastomosis between the bowel and liver. Such leaks resulted in fatal peritonitis in several animals until the present method of anastomosis was adapted. In the introduction of the first suture line, which consisted of a continuous No. 3-0 chromic catgut suture, the edge of the opening in the bowel was approximated to the edge of the cut surface of the transplant. The posterior portion of the open anastomosis was a continuous running stitch which was converted to an inverting Connell suture anteriorly. In this phase of the anastomosis it was important to get a fairly large "bite" of the liver by the suture needle, and to pull the suture up snugly but not tightly. If one or both of these precautions were not followed, the likelihood of necrosis of a portion of the edge of liver forming the anastomosis was increased. Such necrosis has resulted in leakage at the suture line and fatal peritonitis.

The outer suture line, consisting of interrupted No. 4-0 silk Lembert sutures, was applied to the seromuscular coat of the intestine receiving graft and to the seromuscular layer of the intestinal flap which held the graft. This was performed whenever the location of the enteric flap would permit, otherwise the Lembert sutures incorporated liver tissue of the transplant.

Initial results have indicated that the grafts contain a very high proportion of hepatic cells and that the architecture in most instances is preserved. Long-term follow-up with detailed description of histologic findings will form the basis of a future report.

SUMMARY

A method of preparing an autogenous transplantation of canine liver is described. A portion of liver lobe 3 to 5 cm. in diameter is replanted in the free limb of a constructed small bowel Roux "Y."

This loop of intestine serves 2 functions besides merely supporting the graft. First, it provides the new blood supply to the transplant. Second, it acts as a conduit for biliary drainage from the graft into the intestinal lumen.

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ABDOMINAL WALL REPLACEMENT

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A CHALLENGING surgical problem can arise after the resection of large abdominal wall tumors. The tissue loss of skin, fascia, muscle, and peritoneum may be very great with the adequate removal of these soft-tissue tumors. The resection of the tumor and the adjacent abdominal wall can be a simple matter of sacrificing the involved structures. The reconstruction of the abdominal wall can be a more complex problem.

Inadequate resections of abdominal wall tumors have been occasioned chiefly because of concern over the abdominal wall defect and its closure. Furthermore, attempts at resection of such tumors have been abandoned mainly because of the dimension of the defect which would remain following the resection, and because of the subsequent problem in the closure of the abdomen. Several prosthetic materials have been used to close abdominal wall defects. These include tantalum gauze, steel wire mesh, and nylon sheet.[2, 3, 4, 5] Autogenous fascial grafts in the form of fascia lata can also be used to fill these defects.

The iliotibial tract of fascia lata, used as a pedicled flap, has been employed in the repair of lower abdominal wall defects with notable success.[8] In a description of the use of the iliotibial pedicle, Wangensteen gives a case report wherein the external fascia of the abdominal rectus sheath was reflected superiorly to fill a defect in the upper abdomen, and the iliotibial pedicle was rotated to replace the reflected rectus sheath.[9] Other lesser fascial pedicles may be established by reflecting the anterior rectus fascia from either or both recti. Also, the external abdominal oblique musculofascial flap may be reflected medially by dividing the lateral, superior, and inferior margins of such a pedicle.[6]

In the event that there may be a large skin and subcutaneous tissue defect as well as the peritoneal musculofascial defect, it will be necessary to cover the fascial graft or prosthetic material replacement with a thick pedicle graft of skin and subcutaneous fat. In order to assure a healthy, self-sustaining pedicle flap of skin and subcutaneous fat it may be necessary to elevate this pedicle 2 or 3 weeks before the extirpative surgery is performed. This will provide the skin-fat pedicle with a good blood supply for primary healing and resistance to infection, a most important consideration in the presence of contamination.

Depending upon the circumstance, each of the above replacement materials and methods can be used to advantage. Of these materials, tantalum mesh

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has been widely used in the repair of hernia defects as well as in the closure of large abdominal wall defects. Its frequent usage in hernia repair has given it a status of familiarity and reliability that the more recently available materials do not yet have. Its availability as well as the ease with which it may be stored makes tantalum a popular replacement material.

In recent years we have come to avoid tantalum mesh in wounds where tumor recurrence is a possibility, particularly where the mesh is used in defects secondary to the removal of fascial and fibrous tumors of the abdominal wall. It has been our observation that fibrous tumor recurrences may grow rapidly along the latticework of the mesh (Case 1). For this same reason we have avoided the use of nylon or cloth materials. Also, these foreign bodies evoke fibrous scar reaction, thereby adding to the problem of detecting and differentiating clinical recurrence from scar formation. The differentiation of scar tissue from fibrous tumor growth is equally difficult at operation. This dense fibrous tissue stimulation may be considered advantageous in the repair of large hernias, however.[5]

A problem in controlling subsequent radiation therapy in the presence of metallic grafts arises because of the variations in the penetrability of the rays through the metal mesh. It is difficult to calculate the amount of back-scatter of the radiation striking the metallic mesh. Thus the intra-abdominal tumor may receive less than the desired calculated dosage of radiation because of the interposed metallic substances. The tissue superficial to the metallic mesh, however, may receive a dose of x-ray in excess of the calculated dose by virtue of the added radiation of the back-scatter, with resulting tissue necrosis.

Naturally one would attempt to avoid using any foreign material in the presence of infection or in potentially infected areas. However, there will be conditions when this principle cannot be maintained. There are references describing the successful use of tantalum mesh in infected wounds.[4]

For large abdominal wall defects brought about by tumor resection which require a graft replacement, we prefer the use of autogenous fascia lata as a free graft. This material is readily available. Only a few minutes are required to prepare the thigh and obtain the fascia lata. There is no foreign body reaction to this tissue and therefore a minimal amount of fibrous or scar tissue reaction is produced. The fascia is strong enough to maintain the viscera within the abdomen. It is smooth and glistening, presenting an environment similar to that of the peritoneum for the viscera, thus minimizing peritoneal adhesions and the chance of intestinal obstruction. Generally speaking, the fascia lata from one thigh will be more than large enough to cover the largest abdominal wall defect. In only 1 case did we feel that the defect was large enough to require the fascia lata from both thighs (Case 3).

A few case reports of sufficient worth as examples of the problem of abdominal wall replacement are presented.

CASE REPORTS

CASE 1.—When E. O. was 9 years old she had an appendectomy. About a year later she developed a firm nodule in the appendectomy scar. This nodule grew rather rapidly and

in 6 weeks measured 7 by 5 cm. The mass was excised in November, 1951, and was interpreted to be "desmoid tumor, low grade fibrosarcoma." The tumor recurred and in May, 1952, was widely excised by means of a full-thickness en bloc excision of peritoneum, muscle, and fascia from the abdominal wall. This excision removed the inferior portion of the right rectus muscle down to the symphysis pubis. The resultant defect of the abdominal wall measured 8 by 6 cm. A strip of tantalum mesh measuring 8 by 6 cm. was used to close this musculofascial defect. Two weeks later it was necessary to operate on this child for intestinal obstruction. The distal ileum was constricted by adhesive bands between the tantalum mesh and the cecum and ileum.

Nearly a year later, in April, 1953, there was a palpable recurrence in the right lower abdominal wall. This was thought to be about 3 cm. in diameter but upon the opening of the abdomen and the inspection of the peritoneal surface of the abdominal wall, it was apparent that the tumor had infiltrated along the entire segment of tantalum mesh. The

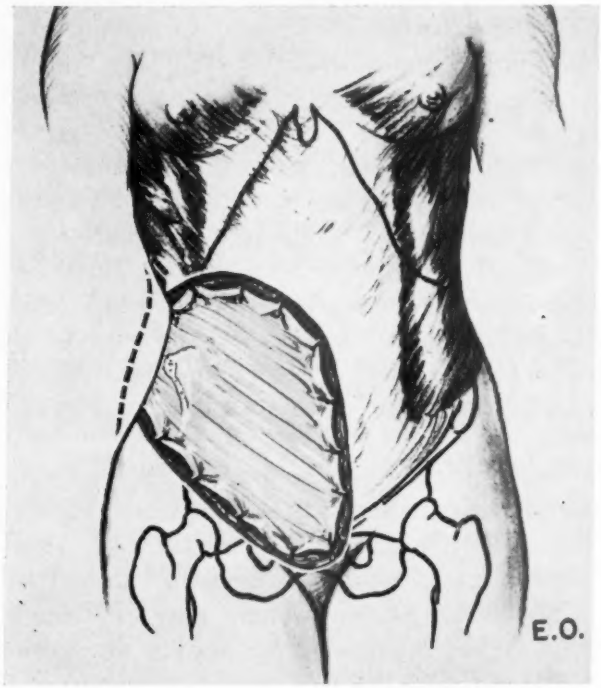

Fig. 1.

tumor and mesh were then excised with the musculature and peritoneum from the level of the umbilicus to the right anterior superior spine and along the course of the inguinal ligament. The defect was filled with a 15 by 9 cm. segment of tantalum mesh. This was covered with the previously reflected skin and subcutaneous tissues. The Pathology Department reported that the specimen was a desmoid tumor, the margins of excision were free of tumor. The desmoid, as determined at operation, was seen to infiltrate throughout the tantalum mesh.

Three subsequent operations were performed within the next 16 months for the removal of recurrences. The greatest abdominal wall defect of peritoneum, muscle, and fascia extended from slightly to the left of the midline well out onto the right flank, including a 4 by 6 cm. segment of anterior superior wing of ileum, thus decreasing the transverse diameter of the anterior abdomen. Vertically the defect extended from just above the umbilicus down to and including the superior ramus of the symphysis pubis. This defect was closed with a free autogenous fascia lata graft measuring 20 by 10 cm. (Fig. 1).

Since this most recent wide excision the child has remained free of disease to the present time, 4 years since her last operation.

In brief, the child had 6 operations for resection of a tumor of the anterior abdominal wall over a 5½ year period. Tantalum wire mesh was used to bridge the defect in 2 of the early operations, but was noted to become infiltrated with the recurrent desmoid tumor.

At this time the strength and contour of the abdominal wall are remarkably normal.

CASE 2.—W. C., a 32-year-old man, presented himself with a recurrent nodular mass of the lower abdominal wall. The tumor mass, most prominent on the left, measured 11 by 20 cm. and was elevated up to 4 cm. During the previous 6 years the patient had undergone 2 local excisions of this tumor and one course of x-ray treatment. His physical examination and laboratory studies were normal.

On Sept. 28, 1956, a full-thickness wide excision of the tumor-bearing portion of the abdominal wall was performed. This excision extended from the left eighth costochondral junction region down to the left inguinal ligament, then transversely across both rectus muscles just above the pubis to an area above the right inguinal ligament. From this point

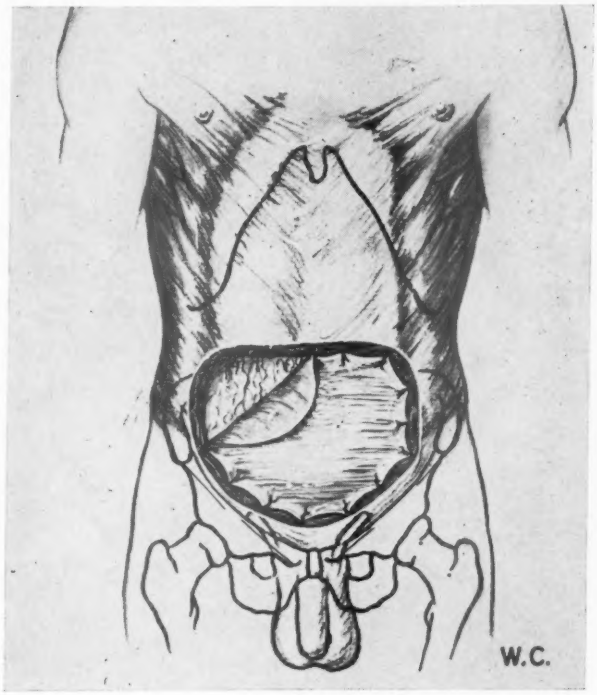

Fig. 2.

the incision extended superiorly to a level above the umbilicus where the excision line was directed transversely to the left to join the first segment of the rectangular en bloc excision, at the left eighth costochondral region.

The skin and peritoneum, as well as all the intermediate tissues, were excised with the en bloc resection. A large sheet of autogenous fascia lata was removed from the right thigh and sutured in place around the periphery of the abdominal wall defect. Inferiorly, where the graft did not reach without tension, the peritoneum and internal oblique fascia were advanced for 2.0 cm. by means of a relaxing incision in the internal oblique fascia. This permitted a fascial covering over the entire anterior abdomen (Fig. 2).

Skin and subcutaneous tissue pedicle grafts were advanced to cover this fascial replacement by means of 2 large thoracoepigastric skin-subcutaneous tissue flaps.

The pathology report indicated dermatofibrosarcoma protuberans.

The postoperative course was entirely uncomplicated. The patient has returned to his work as a postman and has had no symptoms referable to the abdominal wall operation.

Examination in January, 1960, 40 months after the abdominal wall replacement with a fascia lata graft, showed no evidence of tumor recurrence. However, the patient does have an epigastric ventral hernia at the superior border of the fascia lata graft.

CASE 3.—V. T., at the age of 36, was operated on in October, 1953, for what was thought to be a "desmoid tumor of the abdominal wall or a urachus cyst." In November, 1955, a rather large recurrence of this desmoidlike tumor was excised with the lower third of the left rectus abdominis muscle.

In March, 1956, he was admitted to Memorial Hospital presenting a palpable tumor of the lower abdominal wall at the site of the previous excisions. This nodular recurrence extended from just beneath the umbilicus down to the symphysis pubis and laterally beyond the lateral edge of either rectus muscle.

Review of the tissue previously removed showed it to be most consistent with "fibrous peritoneal mesothelioma." There was no evidence of distant metastases by clinical or laboratory examination. An en bloc resection of the lower anterior abdominal wall was performed by incising the skin around the previous low midline incisions. The skin was

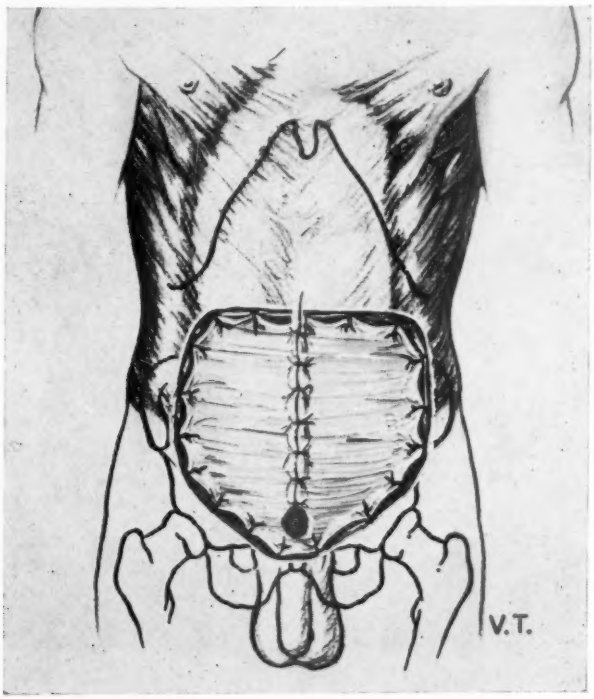

Fig. 3.

reflected laterally exposing the external oblique fascia. Superiorly the abdominal wall was divided through both rectus muscles, fascia, and peritoneum at a level just superior to the umbilicus. This dissection was extended inferiorly at the lateral edge of both rectus muscles, and on the left was extended to encompass the cord structures. The dome of the bladder was attached to the tumor mass, requiring the resection of the anterior superior half of the bladder in continuity with the anterior abdominal wall and the superior rami of both pubic bones. The superior rami of the symphysis pubis were removed because of questionable involvement with the fascial infiltrative tumor. The abdominal wall defect of peritoneum, fascia, and muscle measured 20 cm. vertically and 17 cm. horizontally. The base of the bladder was closed over an indwelling straight catheter. Fascia lata grafts were taken from both thighs and sutured together along the vertical edge to form a sheet of fascia large enough to close the defect left by the removal of muscle, fascia, and peritoneum (Fig. 3). The skin was mobilized laterally, enough to advance a wide pedicle of skin and subcutaneous fat, to cover the fascial graft.

Bladder function rapidly returned to normal after the removal of the catheter on the sixteenth day.

The pathology report stated, "Highly anaplastic spindle cell sarcoma invading the urinary bladder and extending to the periosteum of the symphysis pubis. No tumor at any margin of the resection."

Several examinations after the patient's discharge from the hospital demonstrated the grafted abdominal wall to be firm and without any evidence of herniation, and to be a very satisfactory support for the abdominal contents.

Eighteen months after the resection of the abdominal wall was performed, the patient complained of pain in the deep left pelvis and of ischiosacral pain. Exploration of this area revealed that the fascial tumor invaded the left posterolateral pelvic wall and the iliopsoas muscle. During this abdominal exploration the fascia lata graft was seen to be firm and intact, and to provide good abdominal wall support.

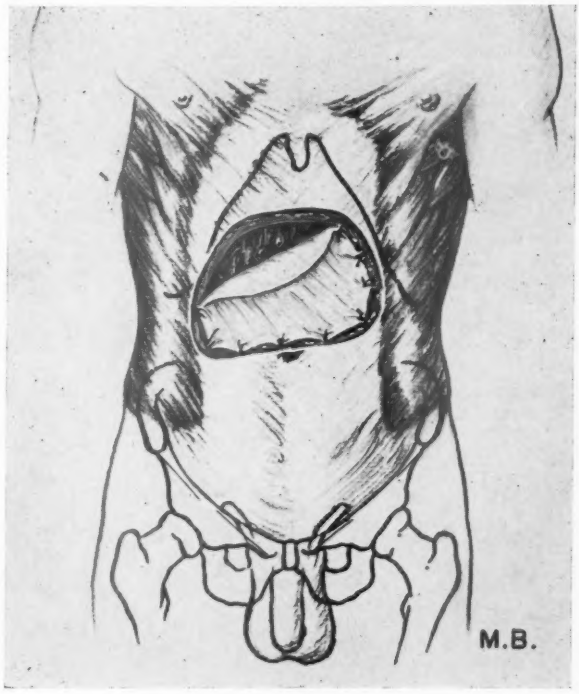

Fig. 4.

The infiltrative recurrence was treated by interstitial radiation in the form of iridium^{192}. The progress of the disease was not notably altered by this radiation and the patient died in February, 1959. The fascia lata abdominal wall replacement remained intact throughout the final 34 months of the patient's life.

CASE 4.—In 1951 M. B. was found to have a carcinoma of the stomach and a subtotal gastrectomy was performed. He stated that he had had no particular symptoms for the first 3 years following operation. He first reported to Memorial Hospital on July 7, 1954, stating that he had noticed a lump in the left abodminal wall for the past month.

Examination revealed him to be a lean, white male in no particular distress. The abdomen was scaphoid and relaxed. There was a 3 cm. nodule in the abdominal wall, to the left of an upper abdominal vertical scar. This nodule was movable. The liver was not palpable, and there was no evidence of visceral or dissiminated metastases.

On July 26, 1954, an exploratory laparotomy was performed using a transverse upper abdominal incision. A large but resectable recurrence of tumor was found extending anteriorly from the duodenal pancreatic area, involving a portion of the transverse colon,

and extending into the anterior abdominal wall. The resection of this large, solitary recurrence was performed by excising a large segment of the abdominal wall, a portion of the transverse colon, and the proximal end of the duodenal stump. With the duodenum closed again and the colon reapproximated, attention was directed to the abdominal wall defect which measured 11 by 20 cm.

A fascia lata graft measuring 24 by 12 cm. was taken from the left thigh and sutured to the peritoneum and fascia at the perimeter of the abdominal wall defect (Fig. 4).

Skin and subcutaneous tissue pedicle flaps were developed from the lateral abdominal wall, superiorly and inferiorly, and rotated over the fascial graft (Fig. 4).

The patient's postoperative course was unremarkable. He gained weight from 134 to 143 pounds. He was able to return to his job as a lithographer and remained well until November, 1955, when he developed a chronic intestinal obstruction, secondary to fixed pelvic metastases.

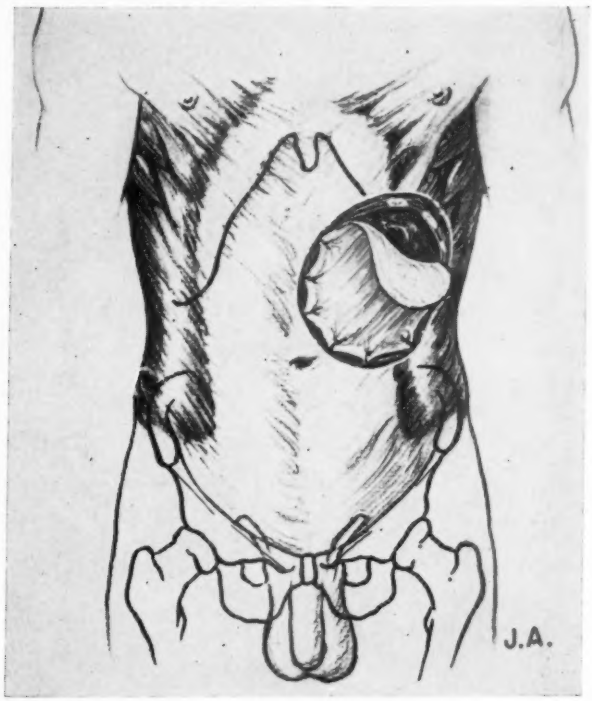

Fig. 5.

He died on April 4, 1956, nearly 5 years after the gastrectomy and 21 months after the resection of a large segment of the anterior abdominal wall and the recurrent tumor. He had been able to return to his work with good abdominal support from his graft for 16 months after the replacement.

CASE 5.—On May 15, 1956, J. A. underwent an extended subtotal gastric resection for carcinoma of the stomach. This resection included the spleen and tail of the pancreas as well as the greater omentum. The pathology report was adenocarcinoma, grade 3, involving all layers of the stomach wall, with lymph nodes negative. The patient's postoperative course was uneventful except for a moderately severe dumping syndrome. Although he did not gain much weight, he was quite well and active.

During his clinic visit in October, 1956, the patient was noted to have a mass involving the left upper abdominal wall. X-ray studies demonstrated a polypoid mass involving the and a second operation was advised. However, in view of his lack of symptoms, he refused splenic flexure of the colon. It was felt that this represented the only site of recurrence to undergo the operation and would not return until March, 1958, nearly 1½ years later.

At the time of his return he presented a huge mass involving the left upper quadrant of the abdomen extending from the lower costal cage to the umbilicus and just across the midline. The splenic flexure of the colon was almost completely obstructed by the mass. On March 21, 1958, after appropriate preparation, an exploratory operation was performed and the mass excised in continuity with the splenic flexure and part of the transverse colon. The mass measured 13 by 15 by 18 cm. A section of colon measuring 20 cm. in length was removed with the tumor mass. This en bloc resection left a defect of all layers of the abdominal wall measuring 15 by 18 cm. The continuity of the bowel was established by an end-to-end anastomosis. The remainder of the abdominal cavity was free of evidence of metastases. The abdominal wall defect was closed by taking a large fascia lata graft from the right thigh and suturing it to the peritoneum and fascia in one layer (Fig. 5). Skin and subcutaneous tissue pedicle flaps were then developed from the chest wall and the abdomen was mobilized over the fascial graft, resulting in a pedicle flap "Z" graft.

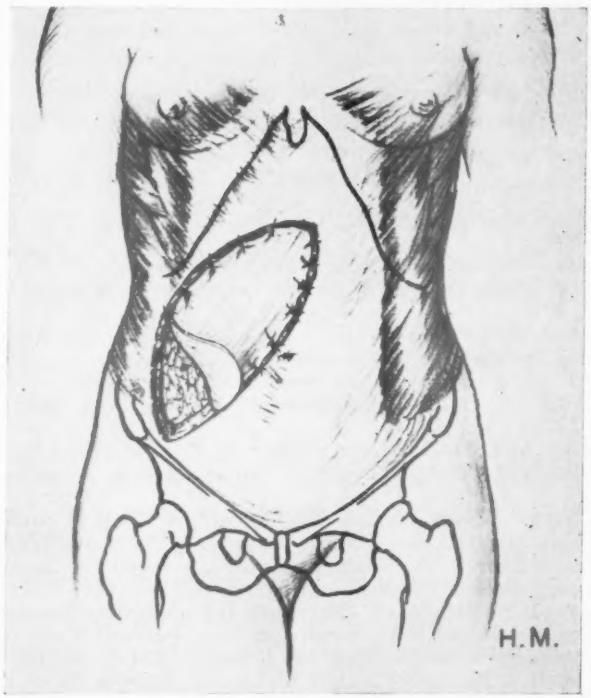

Fig. 6.

The pathology report was adenocarcinoma, grade 3. The postoperative course was uncomplicated and the patient was discharged on the fourteenth postoperative day.

Although the patient gained 10 pounds after his discharge from the hospital, his dumping symptoms persisted. He was free of pain, however. He died of disseminated disease in November, 1958. The area of operation and the graft site were free of disease, and the graft area was firm in its abdominal support.

CASE 6.—H. M. was a 68-year-old graduate nurse who had had Von Recklinghausen's disease since childhood. Two years prior to her admission to this hospital a sarcoma was excised from the right upper abdominal wall. The tumor rapidly recurred and she was given x-ray therapy, but with no apparent effect on the recurrence. Again the tumor was excised, and a recurrence developed within a month.

Initial examination in this hospital revealed widespread skin and subcutaneous neurofibromas. In the right upper quadrant of the abdomen, just beneath a vertical incision scar, there was a mass measuring 10 by 15 cm. This mass invaded almost the entire right abdominal wall, extending to the midline and inferiorly down to the umbilicus. The mass seemed to reach well into the abdominal cavity.

Chest films showed no evidence of pulmonary metastases. Intravenous pyelograms demonstrated a normal urinary system. Barium enema demonstrated the transverse colon to be displaced inferiorly by extrinsic pressure of the bulky tumor. Results of hematologic and blood chemical studies were within normal limits.

On Nov. 4, 1958, the tumor mass was removed with a 3 cm. margin of apparently normal abdominal wall at the periphery. The mass extended into the abdominal cavity and although it did displace the stomach, colon, and small bowel inferiorly and to the left, it did not appear to invade these structures.

The excision left a full-thickness defect of the abdominal wall measuring 18 by 12 cm.

A free fascia lata graft was taken from the thigh and sutured in place to provide an intact closure of the abdominal cavity (Fig. 6).

The skin and subcutaneous tissues of the upper abdomen were mobilized and the graft covered by advancing the skin and subcutaneous tissue. Healing was uncomplicated and the patient had a strong, firm abdominal wall which supported the abdominal contents completely. The pathology report showed neurogenic sarcoma (malignant neurilemmoma).

Within three months the patient developed intraperitoneal tumor in the left peritoneal area. Her condition deteriorated rapidly and she died in February, 1958.

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OBSERVATIONS ON ARTERIOLAR DISEASE IN ARTERIOSCLEROSIS OBLITERANS

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THE study of the pathologic changes in the large and medium-sized arteries in limbs amputated for arteriosclerosis obliterans has provided a great deal of information as to the natural course of the disease.[5, 7, 9, 11] One interesting fact noted by Rodda[9] is that extensive involvement may occur without clinical evidence of disease. The relationship between the location of major artery obstruction and site of tissue death is often not constant.[2, 3]

The probability that arteriolar disease may play a part in the genesis of local tissue death was considered. With full realization that the physiologic consequences of anatomic changes can be only inferred, a histologic study of the arterioles in limbs amputated for arteriosclerosis obliterans seemed worth while.

METHODS

Fifteen amputated limbs from cases of arteriosclerosis obliterans and one limb amputated for Buerger's disease were studied. The age range of the patients was 43 to 72 years. There were 15 men and one woman. Eight patients in this group had diabetes mellitus. The indications for amputation were ulceration and gangrene in 15 cases and rest pain in the remaining case.

The major vessel changes were studied radiographically and by serial section of the major vessels. The radiopaque injection mass used is that described by Schlesinger in 1957.[10]

Sections for histologic study were taken in a systematic manner from the areas supplied by the major arteries. In each instance the sections included skin, subcutaneous tissue, muscle, and selected areas of the major arteries. The sections were stained with hematoxylin and eosin and, in some instances, with Weigert's resorcin fuchsin elastica stain.

The arterioles were classified as being normal or showing minimal, moderate, or severe changes. No specific method of classification other than the impression of the observer was applicable.

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Fig. 1.

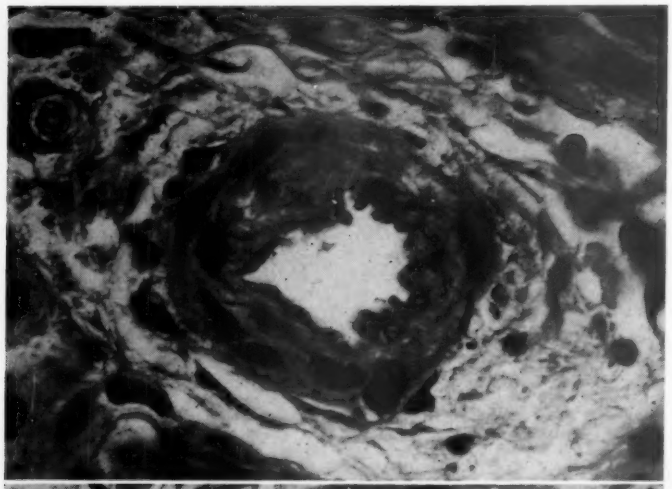

Fig. 2

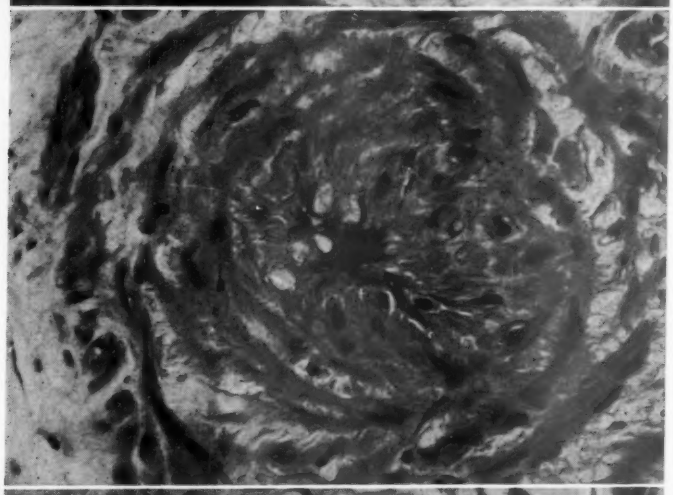

Fig. 3.

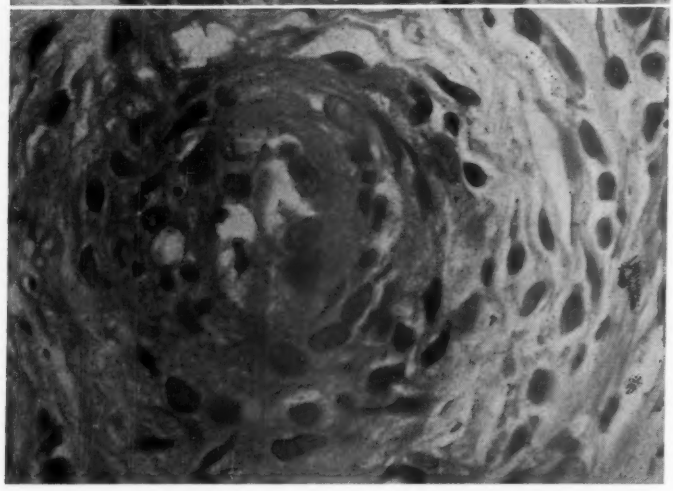

Fig. 1.—Normal arteriole illustrating the cellular media with normal appearing intima and adventitia. (×950; reduced ½.)

Fig. 2.—Severe intimal proliferation with complete obliteration of lumen. Note the foam cells in the subintima and in the region of the media. (×770; reduced ½.)

Fig. 3.—The lumen is completely obliterated by intimal proliferation. Note the foam cells. (×1,200; reduced ½.)

For controls, sections were taken and stained in the same manner from 4 autopsy cases. These sections consisted of skin and subcutaneous tissue. These cases had no clinical or autopsy evidence of significant arteriosclerosis (Fig. 1).

RESULTS

Major Artery Disease.—In each case major points of occlusion were observed. Frequently one limb would show several points of obstruction. The patients with diabetes mellitus generally had more extensive involvement of the large arteries but this was not constant.

Arteriolar Disease.—In this study the arterioles in the 40 to 150 micron size range were given special attention. All of the limbs in this series showed alterations in the arterioles. The vessels showing the most severe changes were located in the dermis and generally the most distal areas of the leg showed the greatest number of arteriolar changes. The changes noted were of two types: (a) proliferative and (b) hyaline.

Proliferative changes were seen in thick-walled vessels with numerous large nuclei in the intimal layer. The smooth muscle of the media was thinned and reduced in amount. The adventitia usually was increased in amount and lamellar in arrangement. The thickened intima was moderately dense but the connective tissue collagen remained in separate strands and took the usual bright eosinophilic stain of active connective tissue. The intima frequently showed subendothelial foam cells (Figs. 2 and 3).

Hyaline changes in the arterioles showed dense, relatively acellular, glassy-appearing walls. The vessels usually showed a smaller lumen but occasionally the lumen did not appear reduced and in a few instances actually appeared increased in relationship to the wall thickness. The media in some cases contained no smooth muscle (Figs. 4 and 5).

Two cases showed severe changes as noted by the degree of change and the number of vessels involved. Eight cases were classified as moderate and five as minimal. The case of Buerger's disease did not show hyaline or proliferative changes.

The arteriolar changes in the patients with diabetes mellitus did not differ in type or severity but the series is too small to warrant definite conclusions.[4]

An additional observation was that of thickening and widening of the collagen bundles of the dermis in the severely involved cases. Also, there was a loss in the eosinophilia of the collagen (Fig. 6). The normal dermis showed thin, wavy, brightly eosinophilic bundles (Fig. 7).

DISCUSSION

Ulcer of the leg due to arteriosclerosis occurring in the presence of hypertension was described by Hines and Farber[6] in 1946. In studying these cases the authors noted that occlusive disease of the larger arteries was not a prominent feature. The changes were postulated to give rise to small areas of superficial infarction with subsequent tissue breakdown and ulceration. The

Fig. 4.

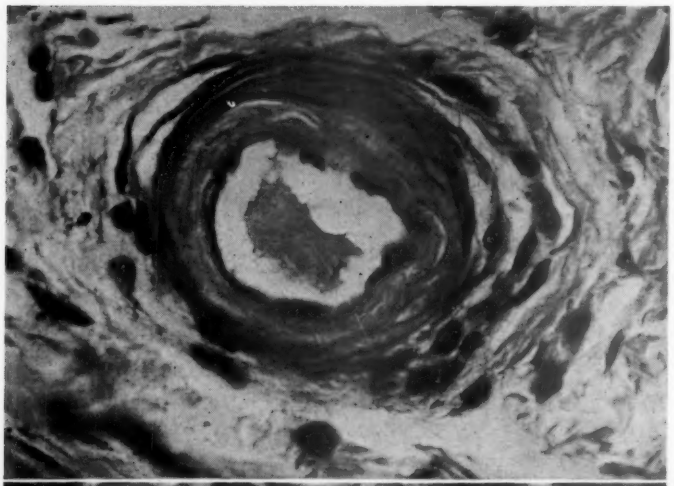

Fig. 5.

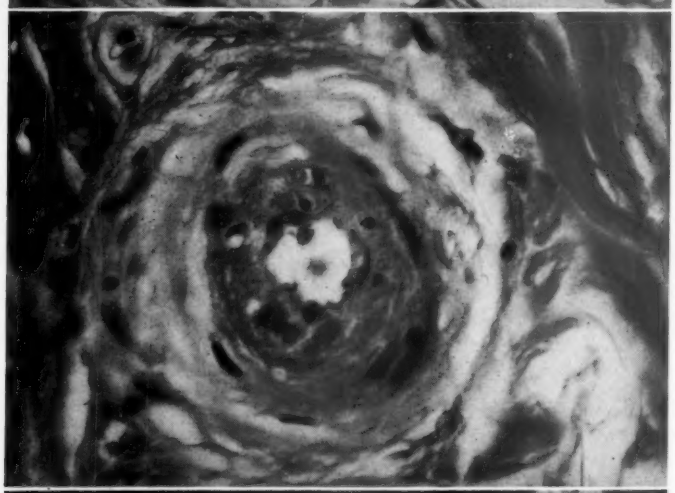

Fig. 6.

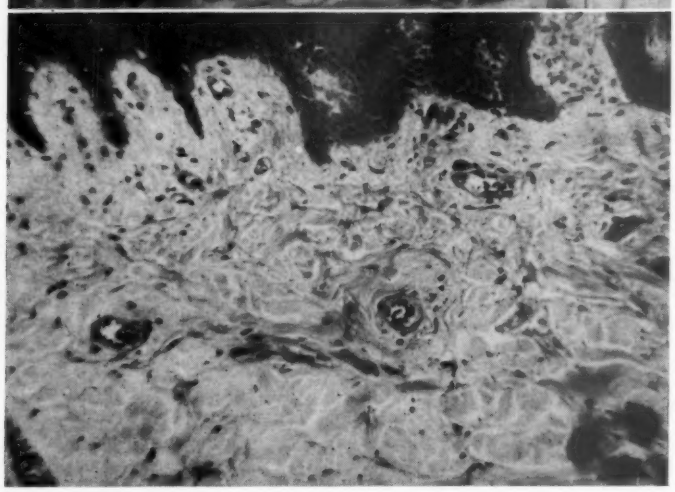

Fig. 4.—Marked hyalinization of the media with complete loss of smooth muscle component. (×1,200; reduced ½.)

Fig. 5.—Marked thickening of the adventitia and hyalinization of the media. (×970; reduced ½.)

Fig. 6.—A case of marked arteriosclerosis obliterans with the dermis showing dense, compact, pale staining collagen bundles. (×250; reduced ½.)

specimens for study were taken from the ulcers and adjacent skin. The changes described were: (1) increase in thickness of wall, (2) decrease in lumen size, (3) increase in number and size of nuclei, (4) hyaline degeneration of the media, and (5) intimal proliferation.

In contrast, the patients in this study were all normotensive and all showed evidence of major artery occlusive disease. Areas of ulceration and gangrene were purposely avoided for study since inflammation, either acute or chronic, might produce changes in the arterioles. The two prominent changes noted in this study were intimal proliferation and hyalinization of the muscular media. The severity of involvement varied and appeared to bear no direct relationship to the degree of major artery disease. As to whether these arteriolar changes precede, follow, or coincide with the major vessel changes cannot be answered at this time.

Fig. 7.—Section of normal skin illustrating loose, delicate collagen bundles of the dermis. (×250; reduced ½.)

Lumbar sympathectomy is the most common operation performed in the treatment of arteriosclerosis obliterations. The success of this operation largely depends upon the state of the arteriolar bed.[1, 8] If the arteriolar lumen is decreased in size by intimal proliferation or if the smooth muscle of the media is replaced by hyaline, the expected response to sympathectomy might not be obtained. These changes could explain the frequent failure of sympathectomy to improve the blood flow to the denervated area.

The resistance to blood flow might be greatly increased in those extremities with arteriolar disease. It is possible that even in situations where major vessel continuity is restored by angioplastic procedures, the capillary bed may not receive adequate blood flow to maintain tissue viability because of the inability of the arteriole to compensate for the increased flow and pressure.

SUMMARY

Fifteen extremities amputated for complications of arteriosclerosis obliterans and one from a case of Buerger's disease were studied for arteriolar disease. Definite arteriolar changes were frequently observed in the cases with arteriosclerosis obliterans. The principal changes noted were intimal proliferation and hyalinization of the muscular media. The therapeutic implications of these changes are suggested.

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FAT EMBOLISM: THE DETERMINATION OF FAT IN THE URINE BY MICROSCOPIC AND MACROSCOPIC METHODS

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THE determination of free neutral fat in the urine is of definite value as a laboratory aid in the diagnosis of fat embolism.[2, 7, 8, 9] Recent investigations[1] in this field led us to standardize and simplify 2 methods of detecting lipuria which, in our experience, have proved very satisfactory, simple, and reliable.

MICROSCOPIC METHOD

Preparation of Material.—The glassware utilized for this determination is rendered fat free by thorough washing with a detergent, generous, successive rinsing in tap water, distilled water, and absolute alcohol, and air drying.

Stain.—Saturated solution of sudan III in alcohol 70 per cent (freshly prepared every 5 days).

Collection of Specimen.—A Foley catheter with a nonoily lubricant is inserted into the patient's bladder and is connected to a 1,000 c.c. volumetric flask. This type of container is used because of its narrow neck which allows a small surface area of urine to accumulate a concentration of fat droplets from a large volume.[4] The flask is allowed to fill until the liquid level reaches the upper portion of the long neck. If the 24 hour output of the patient is not sufficient to do this, tap water is added to this level. Since fat will float on the surface of the urine, overflow has to be avoided. The flasks are stored in the refrigerator overnight and are then processed.

Procedure.—A clean glass slide is marked on the underside with a square. The meniscus of urine in the flask is skimmed with a 3 mm. platinum loop[4] and its contents are smeared within the square on the top of the marked slide. Several slides are prepared in this manner with urine from each specimen. The slides are permitted to dry, the square is covered with several drops of the staining solution, a cover glass is applied, and the marked area of the slide is immediately examined under the microscope (×10) since the stain is picked up by the fat within seconds. The stained specimen should not be allowed to dry before examination.

Results.—Fat appears as deep orange-colored droplets of variable size. The fat droplets are easily distinguished from stain particles by their shape.

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MACROSCOPIC METHOD

Gohrbandt,[3] investigating the presence of nonphysiologic embolic fat in the bloodstream of patients suspected of having fat embolism, developed a staining technique utilizing Nile blue sulfate as a specifically selective dye. This method, as applied to blood, has many limitations and is impractical in most instances. We have adapted Gohrbandt's method to the detection of fat in the urine with success and accuracy.

Collection of Specimen.—Same as for microscopic method.

Stain.—Aqueous solution of Nile blue sulfate 1 per cent.

Procedure.—(1) Five drops of the staining solution is dropped on the urine surface in the neck of the volumetric flask. (2) After 2 minutes 5 drops of ether are added. (3) Two to three minutes is allowed for the evaporation of the ether, after which the walls of the flask above the meniscus of urine are examined with a magnifying hand lens against a white background. Adequate incident light should be available.

Results.—If present, fat is found as small droplets of pink to deep red color precipitated against the wall of the flask a few millimeters above the meniscus of urine.

DISCUSSION

The described staining method utilizing sudan III represents a definite simplification of previous methods.[9] Our experience with it has brought out several notable facts: (1) 24 hour specimens are not strictly essential; (2) it is not necessary to empty completely the bladder on obtaining the specimen; (3) the identification of the fat droplets depends on color and shape and not on size, since smearing with the platinum loop will break up larger droplets and eventually coalesce small ones; and (4) staining occurs within seconds. The Nile blue method, to our knowledge, has not been applied previously to detect lipuria. Besides being a specific stain for lipids, Nile blue also exhibits a definite selectivity by staining neutral fat red, fatty acids blue, and leaving other lipids colorless,[5, 6] a feature of significance for differential diagnostic purposes.

Both methods are simple and easy to carry out without any special or elaborate equipment. Only 1 stain is required in each instance. The results are easy to read and interpret. When both methods are used in conjunction, it is necessary that the Nile blue method follow the microscopic method. Studies are currently under way correlating the proportional sensitivity of these 2 methods. Both methods are qualitative and have no quantitative significance.

SUMMARY AND CONCLUSIONS

1. A microscopic and a macroscopic method for the detection of free fat in the urine are described.

2. The microscopic method uses sudan III as a fat stain and represents a simplification of previous methods.

3. The macroscopic method utilizes the specificity for lipids exhibited by Nile blue sulfate.

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PLATINUM MICROELECTRODE UNIT FOR MEASURING TISSUE OXYGEN TENSION

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A COMPACT single unit composed of a platinum microelectrode and a small calomel electrode has been developed for use with a modified standard polarographic circuit to measure changes in oxygen tension in muscle and other tissues. The electrode has been used effectively in experimental animals and has clinical application to the study of peripheral vascular phenomena and disease in patients.

Heyrovsky[1] introduced the present-day polarographic analysis for determination of reducible and oxidizable substances. The use of stationary platinum electrodes for the study of current-voltage relationships was pioneered by Salomon[1] in 1897. Two basic types of platinum electrodes have been applied to polarographic measurements. Although the rotating electrode has certain distinct advantages, the stationary type is more practical for measuring oxygen availability in body organs and tissues.

The application of a potential across the platinum electrode results in reduction of tissue oxygen at this cathode. The current resulting from this reduction is proportional to the concentration of oxygen in the media in the immediate vicinity of the electrode tip. The calomel cell and the silver–silver chloride cell have both been used as anodes to complete the circuit, since a nonpolarizable electrode is necesary to prevent variations in potential difference.

Polarographic determinations have been carried out in a variety of organs and tissues in both experimental animals and in human beings in an effort to determine alterations in oxygen availability. In most instances the anode was implanted at a distance from the platinum cathode. Montgomery,[2] in the study of oxygen potential of the skin, completed the current circuit by immersing the finger or toe into saline which was in contact with the calomel cell anode. The electrode unit which we have developed has the advantage of combining the platinum cathode and the standard calomel anode. The two electrodes may be introduced through a single small incision with relative ease and negligible tissue damage. These obvious advantages, coupled with the extreme portability of the unit, facilitated its adaptation for clinical use, particularly in evaluating the patient with peripheral vascular disease.

APPARATUS

The electrode we have designed has been manufactured by the Beckman Instrument Company, Fullerton, Calif. (Figs. 1 and 2). The cathode consists

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of a No. 28 gauge platinum wire coated with methylmethacrylate, leaving a 2 mm. bare tip. A small standard calomel half-cell with saturated KC1 serves as

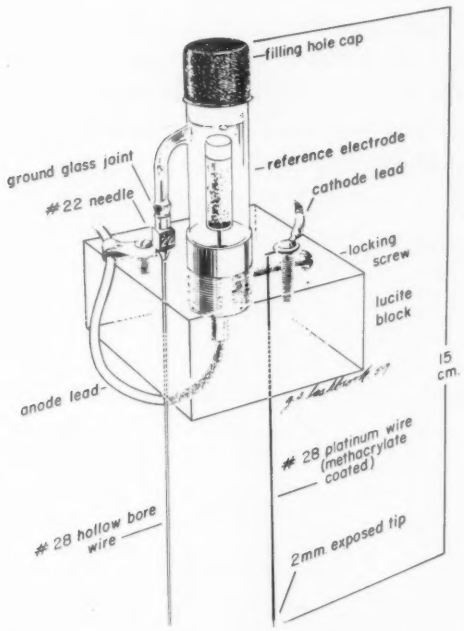

Fig. 1.—Construction diagram of platinum cathode–calomel electrode unit.

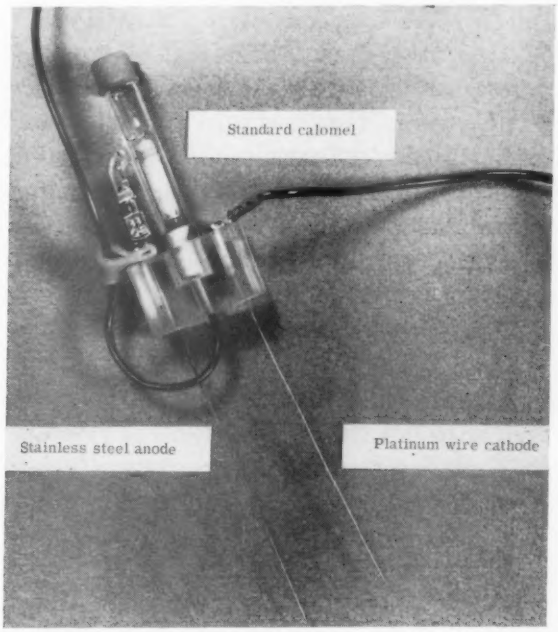

Fig. 2.—Photograph of platinum cathode–calomel electrode unit.

the reference anode. The actual contact arm of the anode is a hollow bore, No. 28 stainless steel wire, which has been passed through a No. 22 needle. The latter fits snugly around a fine ground glass joint, extending from the arm of the calo-

mel electrode so that there is a continuous column of KC1 solution in the hollow bore and in contact with the tissue to be measured. The platinum wire and calomel cell are encased in a Lucite block and the leads extending from these electrodes are plugged into a polarographic unit which permits the application of a constant EMF, and the measurement of the current changes resulting from the reduction of oxygen at the platinum electrode. Fig. 3 illustrates a typical recording from a dog in which the electrodes were implanted in the gastrocnemius muscle. Alterations in muscle tissue oxygen tension were effected by occlusion of the blood vessel and by administration of a known vasodilator, papaverine. In this preparation, the changes in tissue oxygen tension are the direct result of alterations in blood flow to the tissue being measured. The electrode has also been applied to the study of oxygen tension changes in brain, liver, kidney, and myocardium.

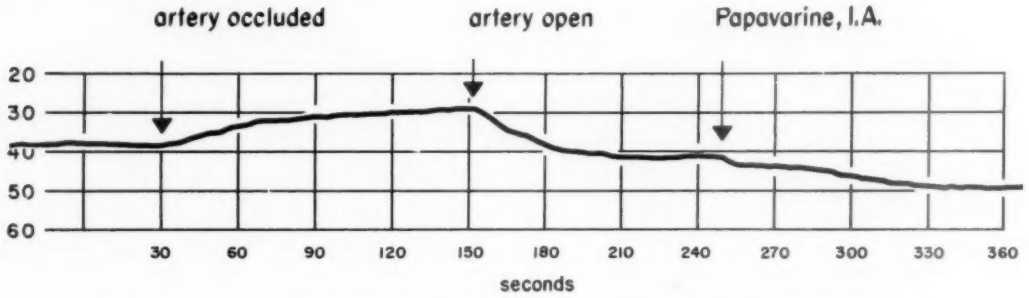

Fig. 3.—Polarographic recording of alterations in skeletal muscle oxygen tension.

DISCUSSION

Although the expression of tissue oxygen tension as an absolute value is at present not practical, the determination of relative changes is of great importance. A significant criterion for the efficiency of a circulatory system is its ability to deliver oxygen at the cellular level. The application of stationary platinum electrode polarography to various organs demonstrates alteration in oxygen availability to the region of the cathode and can be used to assess the effects of vascular occlusion, spasm, and the more commonly advocated vasodilator drugs. The compactness of this portable unit, and the ability to insert both electrodes into the skeletal muscle of an extremity through a minute incision will greatly enhance the study of peripheral vascular disease. Similarly, the unit will facilitate measurement of tissue oxygen tension in the kidney, liver, brain, and other organs.

SUMMARY

A compact unit is described for use in polarography to facilitate measurement of tissue oxygen tension in skeletal muscle, brain, and visceral organs.

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COMPLICATIONS ASSOCIATED WITH DIAGNOSTIC BARIUM ENEMA

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THIS review of the complications and dangers of the diagnostic barium enema was prompted by events which occurred in the instance of a 65-day-old, premature male child. The child was marantic and, despite severe diarrhea, the abdomen was markedly distended. A barium enema was requested.

Roentgenoscopic examination performed by a radiologic house officer was considered to be negative. The enema tube was clamped and films were made. When the filming procedure had been completed, the child began to vomit barium. The films which had been taken showed barium in the colon, in the small bowel, in the stomach, and in the lungs (Fig. 1).

It was found that the clamp on the enema tubing had become dislodged and that barium had been running during the filming procedure, obviously without the knowledge of the technician or the physician. The patient died 3 days later.

Autopsy showed a most severe form of purulent bronchitis and peribronchial pneumonia. Amorphous crystals of barium sulfate, both free and in macrophages, were to be seen in the small bronchi and in the alveoli. The uninvolved alveoli showed a compensatory emphysema.

There were no anomalies of the gastrointestinal tract to suggest that an unusually rapid reverse transit of the barium should have occurred. The liver showed the usual fatty changes of the marantic infant.

This catastrophic consequence of a relatively trifling mishap, the dislodgment of the tubing clamp, was discussed with radiologists from a number of clinics in various parts of the country. It would appear that this experience is not unique and that an easily understood reticence has prevented previous discussion of misfortunes of this type. In 1 instance the sequence of events as described above was said to have been precisely duplicated in another institution. Another instance also concerned a moribund infant, premature in this case, with what was believed to be a lower bowel obstruction. An emergency enema was performed. While radiologist, surgeon, and x-ray technician were in the dark room viewing "wet" films, the clamp on the enema tubing broke. The cecum ruptured with a fatal outcome. A third instance involved a 2½-year-old child who was suspected of having an intussusception. The colon was visualized by barium enema and no intussusception was found. It was decided (an indefensible decision) to attempt to visualize as much of the small bowel

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as possible to eliminate the possibility of a small bowel intussusception. During the examination the patient began to vomit barium and was seen to aspirate some. Barium was found in the entire small bowel, stomach, and esophagus. This patient was fortunate and made an uneventful recovery.

In these cases, all involving children, the complications resulted from the use of faulty technique. In 3 instances the difficulty was with the clamp on the enema tubing, and in the fourth it was the result of an ill-advised attempt to pursue a putative intussusception of the small bowel. Risks from tubing-clamp difficulties can be eliminated by the routine lowering of the enema can to table top level during the filming procedure or when the barium is no longer being administered. With respect to the intussusception, of course, barium enema is not to be relied upon for diagnosis of intussusceptions proximal to the ileocecal valve.

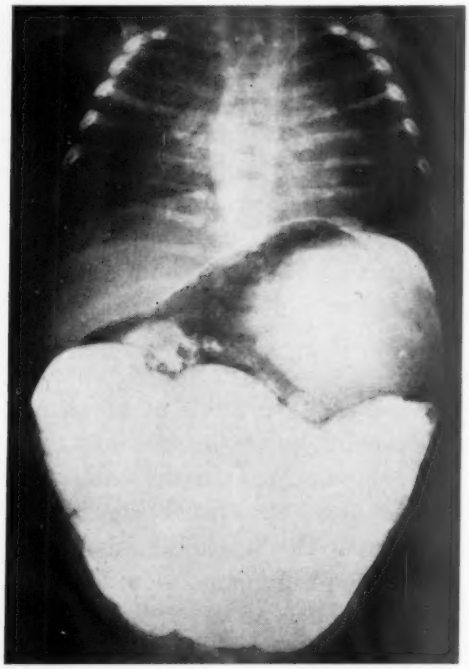

Fig. 1.—Anteroposterior films of the abdomen and chest showing barium in the entire intestinal tract. Photographic reproduction makes it difficult to see the barium in the lungs but this was clearly evident on the original film.

PERFORATION OF THE COLON

The possibility of a rupture of a diseased colon is well recognized. Burt[2] reported the results of an intensive study in which he determined the amount of pneumatic pressure that the normal bowel could withstand. He studied autopsy specimens of apparently normal bowel and demonstrated that the effect of pressure was first the rupture of the outer muscular coats of the bowel wall. The rent was longitudinal and caused a hernia in effect, which in turn ruptured as pressure was increased. Burt found that on the average it required 3.49 lb. of pressure per square inch to rupture the outer coats of the bowel, and a total of 4.07 lb. per square inch to rupture the mucosa. He found that the rectum

supported the greatest intraluminal pressure followed in order of decreasing resistance to pressure by the sigmoid, ileum, esophagus, jejunum, transverse colon, cecum, and stomach.

Calculation shows that under the circumstance of a 3 ft. elevation of the enema can above the table top, and with 300 Gm. of barium per liter of solution, the pressure at the enema tube tip is approximately 1.49 lb. per square inch. This was well under half the average pressure required to initiate rupture of the outer coats of the bowel and well under half of that required to rupture the full thickness of the bowel wall. In clinical practice, elevating an enema can or increasing the specific gravity of the enema mixture will increase the pressure of a fluid administered to the bowel.

Any organic lesion which weakens the bowel wall may be disposed to perforation. Diverticulitis, carcinoma, ulcerative colitis, appendicitis, and amebic abscess may all act in this way. A relatively high incidence of perforation appears to have been observed in barium enemas performed upon patients with pre-existing colostomies. Since the diagnostic barium enema is frequently performed with scant knowledge of the probable nature of the existing pathologic process, one cannot very well anticipate the instances in which a ruptured colon is most likely to occur. This, therefore, indicates the necessity for extreme care in all examinations. Excessive hydrostatic pressure is to be avoided. Palpation should be gentle. The radiologist should consciously recollect that the lead-gloved hand is a heavy one and, particularly in the aged and debilitated with weak abdominal walls, may readily transmit a very sharp increase of pressure to the fluid trapped in a loop.

In addition to the numerous diagnostic studies during which perforation of the bowel occurred, other diagnostic studies have been performed on patients with colons perforated prior to the radiologic diagnostic investigation. Isaacs[6] describes massive peritoneal extravasation of barium in 2 such instances. In neither did plain films show free air within the abdomen. One was an instrumental perforation.

If there is a likelihood that the colon is ruptured, a barium enema study is obviously contraindicated. Zheutlin, Lasser, and Rigler[10] reported 51 per cent mortality in their series of ruptures of the colon in association with barium enema. They point out that results were best when operation was carried out within 3 hours of the rupture and that the mortality rate rose sharply during the next 9 hours.

Diagnosis should usually be quite apparent clinically to the radiologist, although it may be obscured in patients with a markedly obtunded sensorium or in the mentally deranged. Regardless of the clinical condition, the existence of a perforation should be discovered by the radiologist in every case, either during roentgenoscopy or on the postevacuation film. Any barium enema patient complaining of abdominal pain should be retained in the radiology suite until the postevacuation film has been seen.

In some instances there apparently has been an escape of large amounts of barium into the free peritoneal cavity without symptoms.[5, 10] Zheutlin, Lasser, and Rigler[10] reviewed 23 patients who had recovered from a ruptured

colon in association with a barium enema and had been followed for 2 months to 5 years. While many of these patients remained asymptomatic despite a permanent retention of a considerable mass of barium in the peritoneal cavity, about 30 per cent of them developed adhesions which caused sufficient trouble to require operation at some later date. The barium tends to become walled off by fibrous tissue in small cysts. At times granulomatous masses develop.

MISCELLANEOUS

For the sake of completeness, some unusual complications of barium enemas are briefly mentioned. Monnet and Sabon[7] described accidental intoxication with dark room chemicals introduced into the enema solution. Perry and Haden[8] reported the retrograde filling of the right side of the urinary tract with barium during an enema study. This patient had diverticulitis of the sigmoid with perforation of the diverticulum into the right ureter and the establishment of a ureterosigmoid fistula.

A case of ureteral occlusion secondary to a barium granuloma was presented by Elliot and Rosenberg.[3] This occurred in a 68-year-old female who was given a barium enema for investigation of a rectal polyp. The barium ruptured into the retroperitoneal area of the rectosigmoid. The patient seemed to recover promptly following a sigmoid colostomy, and drainage of the perirectal tissues. After 6 weeks she developed oliguria and became comatose. At operation there was found a dense, inflammatory mass in the retroperitoneal tissues and behind the bladder encasing the ureters. The problem was solved by the insertion of indwelling ureteral catheters and subsequent ureteral dilatation.

Beddoe, Kay, and Kaye[1] studied a patient with a barium granuloma of the rectal wall, thought to have been caused by trauma during a barium enema with an extravasation of barium into the tissues of the rectum.

Barium passed into the systemic venous drainage of the rectum with fatal outcome in a patient reported upon by Roman, Wagner, and Steinback.[9] At autopsy there was no gross abnormality to be found in the colon, but barium was found in the hemorrhoidal and hypogastric veins, as well as in the inferior vena cava. It is presumed that the inflation of the Bardex balloon used in association with the enema may have caused a hemorrhoidal varix or a vessel in a fissure to have been held open.

Goldberg[4] described retroperitoneal emphysema, secondary to a double-contrast enema.

SUMMARY

Attention is directed to the danger, particularly to infants, during barium enema. Leaving the enema can elevated and connected to the rectum when the patient is not being watched or while he is being fluoroscoped may result in overfilling of the entire gastrointestinal tract, aspiration, and death.

Other hazards of the barium enema are perforation of the colon into the free peritoneal cavity, perforation of the colon into the retroperitoneal tissues with granuloma formation, barium extravasation into the systemic venous system, and poisoning with dark room chemicals introduced in the barium solution.

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REGIONAL ILEITIS COMPLICATED BY ADENOCARCINOMA OF THE ILEUM: A REPORT OF TWO CASES

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IN 1955 Hughes[4] reported a case of reticulum cell sarcoma, possibly originating in regional enteritis. This was the first report to appear in the literature indicating the possible coexistence of intestinal malignancy with this inflammatory disease. Shortly thereafter, Ginzburg and associates[3] published a case of adenocarcinoma of the jejunum occurring in regional enteritis. Since that time, 6 additional cases of this type have been reported in fairly rapid succession.[1, 2, 5, 7, 8, 10]

At the Cedars of Lebanon Hospital, 2 cases of adenocarcinoma of the ileum associated with regional ileitis have been encountered during the past 12 months.

CASE REPORTS

CASE 1.—E. W., a 61-year-old white female, was admitted to the Cedars of Lebanon Hospital on Dec. 30, 1958, with nausea, vomiting, fever, abdominal pain, and distention, all of 1 week's duration. She complained of recurring bouts of cramplike pain in the left upper quadrant, associated with continuous low grade fever.

Physical examination: The patient was a well-developed, well-nourished female with moderate abdominal pain.

Blood pressure was 128 mm. Hg systolic and 82 mm. Hg diastolic. Temperature was 37.0° C. and pulse rate was 80. The head, neck, chest, and extremities were normal. Abdominal examination revealed marked generalized distention, hypoactive bowel sounds and minimal tenderness throughout the upper quadrants. The rectal examination was unremarkable.

A roentgen survey of the abdomen revealed multiple distended loops of small intestine with very little air in the colon, indicating the presence of a mechanical obstruction of the small intestine and laparotomy was advised.

Operation: There were 200-300 c.c. of serosanguineous fluid in the peritoneal cavity. Most of the small intestine was markedly distended. There were many fluid-filled loops. The serosa was hemorrhagic and dusky and the mesentery contained many large, soft lymph nodes. There was 1 thick, fibrous band completely obstructing the ileum 23 cm. proximal to the ileocecal valve. Beginning 3 cm. distal to this band, the remaining 20 cm. of the terminal ileum was thickened and the serosa was encroached upon by mesenteric fat. In addition, at a point approximately 5 cm. distal to the obstructing band, a discrete mass 2 cm. in diameter which appeared neoplastic was palpated within the thickened ileum. The diseased segment of terminal ileum was resected and a temporary ileostomy was created.

The postoperative course was smooth and uneventful until the fourteenth day when the patient suddenly became dyspneic and died. Autopsy showed massive pulmonary embolism to be the cause of death.

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Pathology: The specimen (Fig. 1) consisted of a 38 cm. length of terminal ileum. The proximal 20 cm. was dilated, thin walled, and filled with fluid. The distal portion was narrowed and its wall somewhat thickened. An abnormal amount of fat encircled the intestine. Near the distal portion of the specimen there was a puckered, firm area where there was a plaquelike thickening on the mucosal surface and an indurated wall. Also included was a 6 cm. indurated mesentery, containing many firm nodes.

Microscopically the involved ileum showed marked ulceration and inflammation with replacement of mucosa by inflamed granulation tissue. Glandular metaplasia of the pyloric type was seen in several foci. The wall was infiltrated massively with lymphoid collections and eosinophils. The plaque showed a diffuse infiltration by neoplastic epithelial cords (Fig. 2) in places with slight glandular differentiation. Transformation from hyperplastic mucosal glands at 1 point was evident. The tumor extended well into the muscular coat. One lymph node showed metastatic carcinoma growing diffusely as mucous cells.

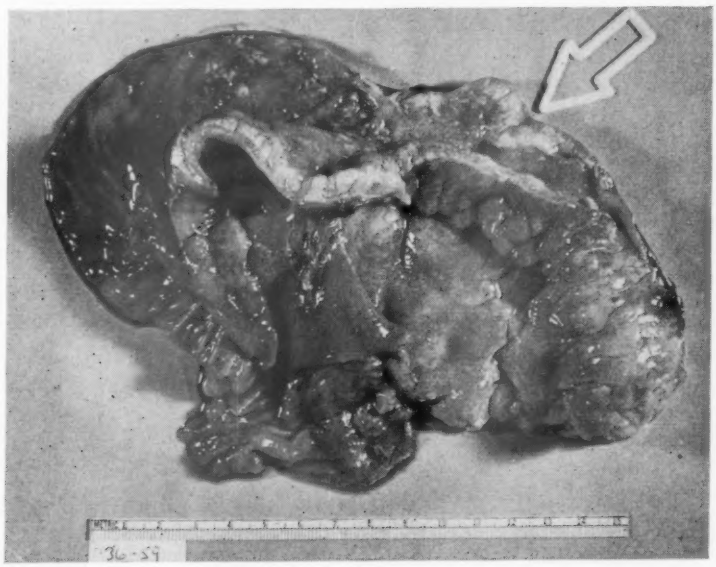

Fig. 1.—Case 1. Gross specimen showing inflamed ileal mucosa and carcinomatous segment.

CASE 2.—K. R., a 62-year-old white female, presented herself at the emergency room of the Cedars of Lebanon Hospital on March 17, 1958, because of a rectal procidentia. Physical examination at this time revealed a firm, smooth, movable, slightly tender, 4 by 4 cm. mass in the right lower quadrant of the abdomen. The patient was admitted to the surgical service for further study.

Past history: The patient had been admitted to the Cedars of Lebanon Hospital in November, 1935, with a history of severe diarrhea, weight loss, and extreme nervousness, all of 17 months' duration. A small intestinal series showed narrowing of the distal 10 cm. of ileum. The patient was operated upon and the involved ileum and cecum were resected with end-to-end anastomosis of healthy ileum to ascending colon. Microscopic examination of the diseased ileum showed changes characteristic of subacute regional ileitis. By July, 1936, the diarrhea resumed, resulting in almost continuous watery stools and a 30 pound weight loss. At this time, barium enema showed a "pipe stem narrowing and spasticity of the terminal ileum." The patient was again operated upon and the involved terminal ileum, ascending colon, and proximal transverse colon were resected. A side-to-side ileotransverse colostomy was performed to restore continuity. Microscopic examination of the specimen showed active regional ileitis.

In early 1948, the patient developed tetany secondary to increasing diarrhea. Despite further supportive therapy over a 2 month period, her condition continued to

deteriorate gradually. A small intestinal series again showed stricture of the terminal ileum proximal to the ileotransverse colostomy and marked distention of proximal loops. Accordingly, the abdomen was re-explored in February, 1949, at which time a transabdominal vagotomy was performed. In addition, the obstructed anastomosis was bypassed with an adjacent side-to-side ileotransverse colostomy in continuity. Examination of the small strips of intestine, which had been excised for anastomosis, showed active ileitis.

Between 1949 and 1958, the patient was seen periodically in the outpatient department complaining of diarrhea, weight loss, ravenous appetite, and a frequently prolapsing rectum, all of which persisted until the present admission.

Physical examination: The patient was an elderly woman who showed evidence of marked weight loss and chronic illness.

Blood pressure was 140 mm. Hg systolic and 80 mm. Hg diastolic. Temperature was 37.4° C. and pulse rate was 88. The head, neck, chest, and extremities were normal. The abdominal examination revealed the previously described mass. Pelvic and rectal examinations were unremarkable.

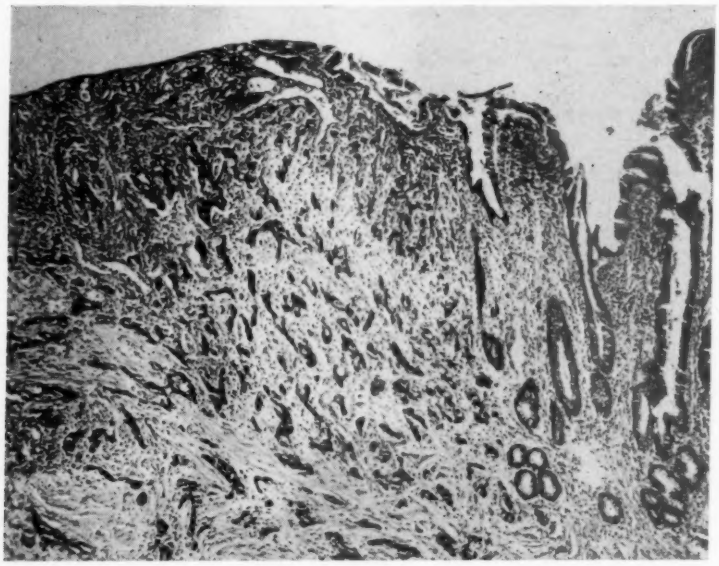

Fig. 2.—Case 1. Shows ileal carcinoma with normal mucosal glands at edge. (×50; reduced ¼).

Barium enema examination showed a filling defect produced by the abdominal mass. The area of involvement appeared to be the proximal portion of the transverse colon, the portion of the intestine distal to this being displaced medially and ending in a blind loop.

Operation: An intraluminal mass at the site of the old anastomosis was found and the distended blind loop of transverse colon was identified just distal to this. Only the terminal 5 cm. of small intestine and proximal 5 cm. of transverse colon showed gross inflammatory changes. The blind loop, terminal 10 cm. of small intestine, old anastomoses, and proximal 8 cm. of transverse colon were resected en bloc. An end-to-end anastomosis was performed to restore continuity.

Pathology: The specimen consisted of a 12 cm. segment of ileum anastomosed to a 10 cm. segment of colon. The anastomosis was open but compressed by a 3 cm. mass which lay between the 2 intestinal segments. Curling around the mass was a 6 cm. blind segment of ileum continuous with a tract lined by friable gray-pink tissue which extended into the central mass. The colonic mucosa was not involved but the ileal mucosa was ulcerated and the wall thickened.

Microscopically, the ileum showed ulceration with a plasmacytic and lymphoid infiltrate. A few foci of acute leukocytic erosion were noted. The wall was fibrotic and studded with lymphoid nodules. The muscle fibers were hypertrophic and the myenteric plexus was so prominent that it suggested neural hyperplasia. The colon showed only

Fig. 3.

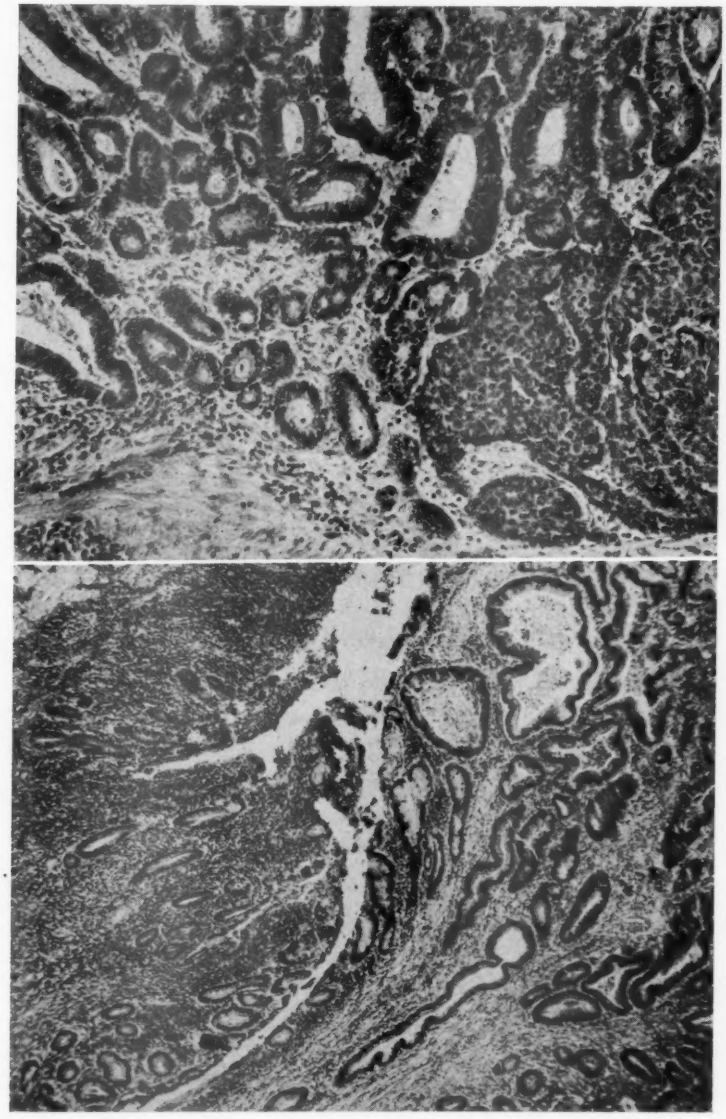

Fig. 4.

Fig. 3.—Case 2. High power view of carcinoma. (×130; reduced ¼.)
Fig. 4.—Case 2. Shows inflamed ileal mucosa and atypical hyperplastic glands. (×50; reduced ¼.)

minor changes. The central mass showed both undifferentiated carcinoma and differentiated adenocarcinoma (Fig. 3) infiltrating the surrounding intestinal walls and fibrofatty tissue. Many small abscesses were present. Foci of atypical metaplasia (Fig. 4) were found in the ileal mucosa near the tumor. The main mass of tumor appeared to be growing from a blind pouch of ileal mucosa, into the lumen of which it had fungated. The nodes were hyperplastic.

DISCUSSION

The first case is a rather self-evident example of the coexistence of adenocarcinoma and terminal ileitis. The knowledge that these 2 entities may appear together in the same segment of intestine was of considerable assistance in resolving the surgical problem which was encountered, extirpation of the diseased segment rather than simple ileostomy.

The second case illustrated long-standing regional ileitis with multiple recurrences over a 25 year period. At the time of the latest hospital admission in 1958, the abdominal mass presented a most interesting diagnostic problem. Since there was no pronounced evidence of an exacerbation of regional ileitis either clinically or radiologically, the possibility of intestinal malignancy was seriously entertained. This fortunately led to exploratory laparotomy.

Prior to 1955, no case of carcinoma occurring in regional ileitis had been reported. Following the publication of cases by Hughes[4] and Ginzburg[3] some attention was given to this rare possibility. Before long, one author stated that the occurrence of malignant change is variously quoted as from 1 to 5 per cent.[6] It was implied that these figures might favor resection as opposed to exclusion in the surgical treatment of regional ileitis. At this time there is insufficient evidence to substantiate these figures and conclusion. However, as previously noted, new cases are appearing rapidly and possibly, in the future, many other cases will be reported so that medical management, surgical indications, and definitive surgical procedures might be altered.

SUMMARY

Two cases of regional ileitis and adenocarcinoma of the ileum occurring together are reported. No case is reported prior to late 1955, and since then 6 other cases were extracted from the English literature. Although it is rare, it is important that clinicians should be aware of this possibility.

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EXPERIMENTAL EVALUATION OF METHODS FOR THE EARLY TREATMENT OF SNAKE BITE

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ALTHOUGH an estimated 2,000 to 3,000 snake bite accidents occur yearly in the United States,[9] the mortality from this source is not great, for only 10 to 20 deaths occur as a result.[12] It is important, however, that bites of poisonous snakes be managed correctly since, in many instances, the possibility of a lethal outcome must be considered and because the venom may damage tissues at the site of injection. Treatment should be chosen which is most effective and which is least likely to lead to deleterious effects itself. In an individual human case, it may prove extremely difficult to determine what part of the local tissue damage has resulted solely from the necrotizing properties of the venom and what part has been caused or abetted by the treatment.

The purpose of this report is to examine 2 techniques currently advocated for management of bites of pit vipers in North America and to compare the efficacy of these measures to that of specific antiserum. The first of the techniques, incision and suction, recommended in both the popular and medical literature, is supported largely by the experiments of Jackson,[2, 3] made 30 years ago. Evidence from more recent experiments has cast considerable doubt on its value.[4, 6, 8] The obvious disadvantages of this method include possible damage to important structures such as tendons and nerves, hemorrhage, and infection when the incisions are carried out by an inexperienced person. When carried out under ideal conditions, the multiple incisions produced must still heal with some degree of scarring. These are considerations to be weighed against the effectiveness of the method in removing venom. The second technique, initial tourniquet application followed by local cooling of the bitten extremity, has been offered both for first aid and definitive therapy[11] and it has been suggested that tissue necrosis at the site of the bite can be reduced considerably if this technique is employed. This method has been condemned however, on the basis that local necrosis may be greater with the application of cold.[10]

METHODS

The effect of treatment has been determined following the injection of venom of the eastern diamondback rattlesnake, *Crotalus adamanteus*. Dried venom obtained from a commercial source (Ross Allen's Reptile Institute) was reconstituted with normal saline to a concentration of 50 mg. per milliliter. Mongrel dogs weighing from 4.5 to 18.2 kilograms were utilized. Injection of venom was made with syringe and No. 23 gauge needle into the subcutaneous tissue

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of the lateral aspect of 1 thigh of the dog. All animals were anesthetized with pentobarbital sodium administered intravenously in dosage of 26 mg. per kilogram prior to the experiment.

The following experimental treatments have been carried out for *Crotalus adamanteus* envenomation:

1. No Treatment.—Survival time has been determined for control animals after venom injection in dosage ranging from 5 mg. per kilogram to 8 mg. per kilogram of body weight.

2. Incision and Suction.—Cruciate incisions with suction of the incised wounds have been utilized either immediately or after a delay of 30 minutes following venom injection. A tourniquet to impede lymph flow was applied around the limb as close to the trunk as possible immediately following venom injection. Cruciate incisions were made over the site of venom injection and in the area of swelling as it developed and suction was applied. An average of 15 incisions was made in the envenomed limb. Suction was utilized for 15 minutes of each half hour period and was continued for 6 hours in most experiments and for 3 hours in a few animals. Twenty milliliter glass syringes with the ends of the barrels cut off smoothly were utilized to provide suction of the incised wounds.

3. Incision and Suction at Site of Injection Only.—Following venom injection 2 cruciate incisions were made ½ inch apart at the site of injection and suction was carried out for a half hour period. A lymphatic tourniquet was applied as in the first experiment.

4. Tourniquet and Local Hypothermia.—Immediately following venom injection, a tourniquet was applied tightly around the extremity as close to the body as possible. The limb was then placed in a plastic bag and packed in crushed ice. After a period of 1 hour, the tourniquet was removed. The limb was allowed to remain packed in ice for a period of 24 hours, or until death of the animal, if this occurred earlier. Rewarming of the limb was achieved slowly at the end of this period by allowing the ice to melt without being replaced.

5. Tourniquet and Local Hypothermia for 8 Hours, Followed by Specific Antiserum.—Following venom injection, local cooling was carried out as in the third experiment. At the end of 8 hours, specific antiserum was given intravenously in dosage calculated to neutralize 4 mg. of venom per kilogram of body weight and cooling was slowly discontinued.

6. Tourniquet and Local Hypothermia for 4 Hours, Followed by Specific Antiserum.—This experiment was identical with No. 5, except local cooling was continued for only 4 hours before antiserum was administered intravenously in dosage calculated to neutralize 4 mg. of venom per kilogram of body weight.

7. Specific Antiserum After Delay of 8 Hours.—Following venom injection, no local treatment was utilized except a tourniquet to impede lymph flow. At the end of 8 hours, specific antiserum was given intravenously in dosage calculated to neutralize 4 mg. of venom per kilogram of body weight.

8. Specific Antiserum After Delay of 4 Hours.—Following venom injection, no local treatment was utilized except a tourniquet to impede lymph flow. At the end of 4 hours, specific antiserum was given intravenously in dosage calculated to neutralize 4 mg. of venom per kilogram body weight.

9. Early Treatment With Specific Antiserum.—Following injection of venom in lethal dosage, antivenin calculated to neutralize 4 mg. of venom per kilogram was given after a 30 minute delay.

In each experiment survival time has been determined to the nearest possible hour if death occurred in the first 48 hours following venom injection. Animals were considered survivors if they lived for 4 days or more. Many animals died of infection or had to be sacrificed after this period because of the widespread gangrene which occurred at the site of venom injection.

Necrosis at the site of injection of venom has been graded as slight, moderate, or severe in degree. If the area of tissue damage was less than 5 cm. in diameter,

it has been considered slight. If it is from 5 to 8 cm. in greatest diameter, involving predominantly superficial tissues, necrosis was of moderate degree. Severe necrosis included all sloughs greater than those described above. Body temperature of the animals utilized in local hypothermia experiments was maintained at normal levels by use of a heating pad but no other supportive therapy, such as the administration of blood or antibiotics, was given in any experiment. Following experimental therapy, animals were returned to their cages and observed until death, recovery, or eventual sacrifice. In all experiments with antiserum, Antivenin (Crotalidae) Polyvalent was utilized and was prepared in accordance with the instructions supplied by the manufacturer.

RESULTS

Studies of control animals injected with *Crotalus adamanteus* venom in dosage ranging from 5 to 8 mg. per kilogram of body weight are shown in Table I and duration of survival is given. In some of the earlier experiments

TABLE I. EXPERIMENTAL CROTALUS ADAMANTEUS ENVENOMATION; NO TREATMENT

NO. OF ANIMALS	WEIGHT (KG.)	VENOM INJECTED (MG./KG. BODY WT.)	DURATION OF SURVIVAL OF EACH ANIMAL (HR.)
6	8.6-17.7	5	6, 12, 13, 16, 2 survived
2	10.0-10.9	6	36, 1 survived
2	11.4-16.8	7	8, 8
9	4.5-14.1	8	6, 9, < 16, < 16, < 16, < 16, < 16 < 16, < 16

utilizing hypothermia, 5 mg. of venom per kilogram of body weight was given as the test dose of venom. That a uniform lethal effect is not produced is evident since 2 of the 6 dogs survived this dose of venom without treatment. In order to insure a fairly uniform lethal effect, a larger dose (8 mg. per kilogram) appears to be necessary and any conclusions concerning effectiveness of therapy in preventing deaths following *C. adamanteus* poisoning must be derived from those experiments where at least 8 mg. of venom per kilogram was given as the test dose. In each control experiment terminating in survival, local necrosis has been severe. Minton[7] has shown the local necrotizing properties of venom of this particular species to be greater than that of any other rattlesnake which he studied.

The results obtained with experimental treatment are summarized in Table II. There appears to be some evidence that incision and suction may increase survival if carried out immediately following Crotalus venom injection. Six of 11 animals treated intensively by this technique survived. In each instance, local necrosis was of severe degree. Two of these dogs received treatment for only 3 hours, the remainder for 6 hours. However, if a delay of 30 minutes occurred before incision and suction was carried out, there were no survivors among 6 animals treated. Five of the total number of animals treated by incision and suction for 3 to 6 hours which died survived for less than 6 hours. Conceivably, the manipulation incident to incision and suction may have increased the rate of venom absorption and hastened the death of these animals. Two of 8 animals survived when treated only by incision and suction at the site of venom injection.

Immediate application of a tight tourniquet to the envenomed extremity followed by local cooling with removal of the tourniquet 1 hour later was carried out in 10 animals. *C. adamanteus* venom was given in dosage ranging from 5 mg. to 8 mg. per kilogram body weight. The skin temperature at the site of venom injection averaged 10° C. during the cooling period. Earlier experiments showed considerable promise, for survival was obtained for 4 of the 5

TABLE II. TREATMENT FOLLOWING EXPERIMENTAL CROTALUS ADAMANTEUS ENVENOMATION

NO. OF ANIMALS	RANGE (WT. IN KG.)	VENOM INJECTED (MG./KG.)	TREATMENT ADMINISTERED	DURATION OF SURVIVAL OF EACH ANIMAL (HR.)
6	6.4-11.8	8	Incision and suction 6 hr., ½ hour delay	14, 36, 11, 16, 5, 6
2	12.7-14.5	8	Incision and suction 3 hr., no delay	18, 1 survived
9	11.3-16.3	8	Incision and suction 6 hr., no delay	5, 6, 12, 5, 5 survived
8	4.5-8.6	8	Incision and suction at site of venom injection for ½ hr., no delay	6, 12, 16, 16, 8, 8, 2 survived
5	9.5-15.9	5	Local hypothermia	16, 4 survived
1	11.3	6	Local hypothermia	45
2	8.6-11.8	7	Local hypothermia	4, 20
2	13.2-18.2	8	Local hypothermia	11, 22
8	6.8-12.7	8	Local hypothermia, 8 hr., then specific antivenin to neutralize 4 mg. venom/kg. body wt.	16, 3 days, 6 survived
7	5.5-14.1	8	Specific antivenin to neutralize 4 mg. venom/kg. body wt., 8 hr. delay	18, 12, 11, 16, 16, 8, 1 survived
8	5.9-12.2	8	Local hypothermia 4 hr., then specific antivenin to neutralize 4 mg. venom/kg. body wt.	48, 36, 6 survived
8	5.4-12.8	8	Specific antivenin to neutralize 4 mg. venom/kg. body wt., 4 hr. delay	2, 48, 24, 5 survived
8	6.8-10.0	8	Specific antivenin to neutralize 4 mg. venom/kg. body wt., ½ hr. delay	8 survived

animals receiving 5 mg. of venom per kilogram. There were no survivors, however, among the remaining 5 animals treated in an identical fashion but injected with larger doses of venom.

The most severe tissue damage of the injected area seen in any experiment occurred in animals treated by this technique. In animals surviving the smaller doses of venom (5 mg. per kilogram) necrosis uniformly involved the entire lateral aspect of the limb, extending into muscle and often exposing the underlying bone. In 2 animals, circumferential slough of the muscles of the leg occurred resulting in gangrene of the entire extremity. It appears, therefore,

that no protection is offered by local cooling against certain, lethal dosage of venom, and extensive necrosis occasioned by localization of venom in the injected area outweighs any advantage which might be obtained with this treatment after venom is injected in lesser amounts.

Local hypothermia, however, appears to be of some benefit as a temporary measure prior to injection of specific antiserum. The extremities of 8 animals which had been injected with 8 mg. of venom per kilogram of body weight were cooled for a period of 8 hours as in the above experiments. At the end of this time specific antiserum was injected intravenously in dosage calculated to neutralize 4 mg. of venom per kilogram of body weight. Six of the 8 animals survived and 1 lived 3 days before death. All 6 survivors showed severe local necrosis at the site of venom injection. This is to be compared with the results of experiments with animals receiving no specific treatment except a lymphatic tourniquet for 8 hours following venom injection in the same dosage. Specific antivenin was then given in dosage calculated to neutralize 4 mg. of venom per kilogram of body weight. Only 1 animal of 7 treated in this manner survived.

There is no evident beneficial effect of cooling, however, if the time period between the injection of venom and subsequent antivenin administration is only 4 hours. A comparison of the data shows no significant difference in survival of animals treated by cooling of the extremity for 4 hours and then given antiserum (calculated to neutralize 4 mg. venom per kilogram of body weight) when compared to those treated with antiserum in the same dosage after a delay of 4 hours with the extremity at room temperature. Five of 8 animals survived when treated by antivenin alone. Two of these 5 survivors treated by antiserum alone had severe necrosis locally. Two developed moderate damage and the other animal showed no gross damage at the site of venom injection. Five of the 6 survivors treated by hypothermia and subsequently with antiserum developed severe degrees of tissue damage of the envenomed limb.

Finally, 8 animals were treated by antiserum alone after a half hour delay. All survived. Three developed no tissue damage locally and 1 animal developed minimal necrosis at the venom injection site. Three animals showed moderate tissue damage.

DISCUSSION

Whether or not data obtained from envenomation experiments in dogs are applicable to the human patient has not been proved. However, autopsy studies and clinical observations indicate the lesions produced and the mechanism of death in the 2 species are similar and some conclusions concerning treatment of patients seem justified. From the foregoing experiments it appears that the local measures studied may be of some benefit in therapy but the availability of antiserum and the period of delay which will occur prior to its administration probably should determine the place of such local measures in treatment of bites of pit vipers.

The local necrosis produced by venom is not decreased by cooling. It appeared, as observed by Allen,[1] that tissue destruction at the site of venom injection was equal to and, in most instances, actually greater than in untreated

animals. Furthermore, no evidence was obtained that local hypothermia is of value as definitive therapy since all animals treated by hypothermia alone died following injection of venom in lethal dosage. Increase in survival was obtained by interim cooling of an envenomed extremity if antiserum administration was delayed for as long as 8 hours, but no benefit was apparent if antiserum was given within 4 hours of venom injection. Since the local necrotizing properties of venom may be increased by cold, and as hypothermia appears at best to serve only as a temporizing measure, considerable caution should be exercised in treating pit viper bites in this manner. Only potentially lethal bites for which antiserum will be available after a delay of some hours should be treated by this method. The increased local tissue damage is the price of survival of the bitten individual. Treatment of bites of small snakes by local cooling appears more likely to be harmful than beneficial since the degree of damage at the site of the bite may be increased.

Results of our experiments are in agreement with those of Parrish[8] that incision-suction treatment of dogs injected with lethal dosage of Crotalus venom is useless if treatment is delayed for a period of 30 minutes after venom injection. In order to obtain surviving animals by this technique it was necessary to institute the treatment immediately. Experiments roughly comparable to recommended first aid treatment (immediate incision and suction at the site of venom injection) led to survival of only 2 of 8 animals treated. Results were somewhat better if the animals were treated immediately and more extensively (average of 15 incisions per limb), but survival rate for this group was no different than for animals treated by antiserum alone after a delay of 4 hours. Since this type of incision-suction treatment is more comparable to that which would be carried out by a physician than to that employed by a layman, circumstances would not often arise where it could be employed in patients with pit viper bites without some delay. The same treatment after a delay of 30 minutes proved useless in animal experiments.

Incision-suction is probably of some benefit in treatment of snake bite. However, the spreading of venom incident to manipulation and the possibility of damage to important structures probably outweighs the value to be gained from first aid measures. Practical considerations make the application of extensive incision-suction treatment extremely unlikely in time to be of benefit. There is no evidence from present experiments that local necrosis is decreased by this measure and if venom is injected intramuscularly instead of subcutaneously by the striking snake, as has been suggested,[12] incision-suction treatment cannot be effective because of the fascial barriers. Main reliance in treatment of pit viper bites should be placed on specific antiserum, and incision-suction treatment should be utilized only in circumstances when no other treatment is available or will be available for many hours.

SUMMARY

1. Dogs have been injected with venom of *Crotalus adamanteus* and experimental treatment carried out. Eight milligrams of venom of *C. adamanteus*

per kilogram of body weight was found to be a satisfactory lethal dose for evaluation of therapy.

2. Local hypothermia was of no benefit as definitive therapy after *Crotalus* envenomation. It was of value in cooling an envenomed extremity in the interim period if specific antivenin administration was delayed for a period of as long as 8 hours. Survival was not significantly increased by interim cooling if antiserum administration was delayed for 4 hours. Local hypothermia resulted in greater tissue damage locally than that occurring in untreated animals.

3. Incision and suction treatment increased survival if carried out immediately following Crotalus envenomation but results were no better than in animals treated with antiserum administered after a delay of 4 hours. If delayed for a half hour, incision and suction treatment was useless.

4. The proper treatment of pit viper bites is administration of antivenin. Local hypothermia and incision-suction treatment would appear to be indicated rarely and only under special circumstances.

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EFFECTS OF CHANGING HEPATIC BLOOD FLOW ON 17-HYDROXYCORTICOSTEROID METABOLISM IN DOGS

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AFTER intravenous infusion of Cortisol, the removal rate of free 17-hydroxycorticosteroids (17-OHCS) from the plasma and the appearance of conjugated 17-OHCS in the plasma will depend on general body metabolism[1] and on the functional state of the liver.[3] In patients with hepatic cirrhosis in whom blood flow to the liver is reduced,[3] and in patients with myxedema, there is a delay in the disappearance of the free 17-OHCS from the plasma and a decrease in the formation of the conjugated 17-OHCS.[1, 7]

In view of the important role played by the liver in the metabolism of 17-OHCS, it seemed of interest to examine the changes which might be produced merely by altering hepatic blood flow. In this study the blood flow to the liver was altered by operation. This made possible an assessment of the effects of increased and reduced hepatic blood flow on the rate of removal of free 17-OHCS from the plasma and on the formation of conjugated 17-OHCS.

MATERIALS AND METHODS

Twenty-three mongrel dogs, ranging in weight from 11 to 31 kilograms, were studied. Over a 17 to 34 minute period, each animal received an intravenous infusion of Cortisol† (1 mg. per kilogram) in 100 to 200 ml. of a solution containing 1 per cent to 2 per cent ethyl alcohol and 5 per cent dextrose.[3, 7] Blood samples for the determination of free and conjugated 17-OHCS levels in the plasma were obtained at 0, 0.5, 1, 2, 3, and 4 hours after the beginning of the infusion.[3, 7] On a different day, per cent retention of bromsulphalein (BSP) was measured in serial samples of plasma for 45 minutes after an intravenous injection of 5 mg. per kilogram. Anesthesia was not required since the animals were trained for all testing manipulations.

In 14 of the 23 dogs hepatic devascularization was produced by a modification of the technique of Rappaport,[11] which consists of an end-to-side portacaval anastomosis through a right thoracoabdominal incision, followed in 2 to 8 days by ligation of the hepatic artery through an upper midline incision. Eight

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†One animal received Cortisol hemisuccinate in similar concentration.

to 22 days after the surgical procedure, when the animals appeared to have their normal preoperative behavior, the Cortisol infusions and BSP tests were repeated.

In 7 animals, arterialization of the liver[9] was performed by establishing an end-to-side portacaval shunt and inserting an Ivalon vascular prosthesis as a shunt between the aorta (below the renal arteries) and the hepatic stump of the portal vein. The standard Cortisol infusion and BSP tests were repeated after a recovery period of 1 to 4 weeks.

In one animal, both hepatic arterialization and devascularization were performed. After the initial arterialization study was completed, the liver was devascularized by ligation of the hepatic artery and the Ivalon shunt.

Nembutal anesthesia was used for all operations. Because of the required number of venipunctures, each animal received 0.2 Gm. ferrous sulfate by mouth daily from the time of selection for study until the last test procedure was finished. Postoperatively, all animals received a daily intramuscular injection of 300,000 U. procaine penicillin and 0.25 Gm. dihydrostreptomycin for 10 days. The animals with devascularization of the liver received a continuous intravenous infusion of B complex vitamins* and 10 per cent dextrose in 0.9 per cent saline solution at the rate of 10 to 80 ml. per hour (usually 30-40 ml.) for 24 to 72 hours following ligation of the hepatic artery. From cessation of the constant infusion to the resumption of feeding, dextrose and B complex vitamins† were added to the drinking water of this group of animals.

A needle biopsy of the liver was performed after the postoperative infusion of Cortisol to detect any histologic evidence of liver damage.

Postoperative studies were excluded if any of the following complications were present: (a) behavior and feeding habits of the animal did not return to normal, (b) jaundice developed, (c) the liver biopsy specimen indicated morphologic abnormalities, or (d) the bruit produced by the patent aorta-portal vein fistula disappeared.

Free 17-OHCS in the plasma were measured by the modified method of Eik-Nes, Nelson, and Samuels,[6] and the conjugated 17-OHCS in the plasma were determined by a modification[2] of the method of Bongiovanni.[4]

RESULTS

Four of the animals subjected to devascularization and 3 surviving the arterialization operations met the criteria for restudy. The remaining dogs did not survive or were excluded for the reasons listed above (a-d).

Plasma concentrations of free 17-OHCS following intravenous administration of Cortisol are shown in Fig. 1. In the 7 animals which completed the entire study successfully and in 4 other normal animals which were not restudied, a mean preoperative (normal state) half-life with 1 standard error of the mean (S.E.M.) of 61 ± 6 minutes was obtained. In the dogs with arterialized livers, the mean half-life was 52 ± 5 minutes, but in the animals with devascularized livers, the mean half-life was 84 ± 13 minutes.

*Two milliliters Berocca-C per liter.
†Two milliliters Berocca-C per drinking bowl.

The mean levels of conjugated 17-OHCS in the plasma after Cortisol infusion are plotted in Fig. 2. In the normal dogs, the peak occurred 1 hour after infusion. Peak concentrations were higher and were observed sooner in samples from dogs with arterialized livers than in those from normal dogs. In the animals with devascularized livers, however, the levels of the conjugated 17-OHCS rose more slowly and did not reach values as high as those in the normal animals.

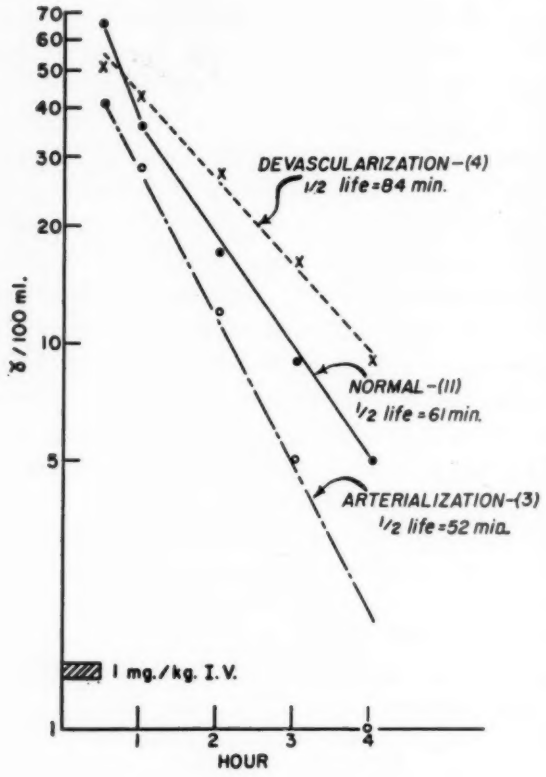

Fig. 1.

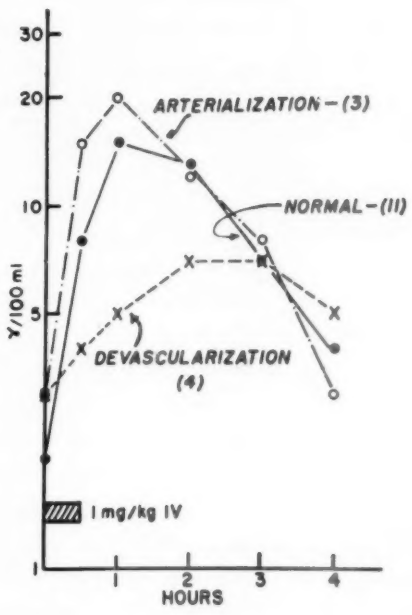

Fig. 2.

Fig. 1.—Semilogarithmic plot of the mean free 17-OHCS levels in plasma after an intravenous infusion of Cortisol. Numbers in parentheses indicate the number of animals in each group. Note the delay in the disappearance of the free 17-OHCS in the dogs with devascularized livers.

Fig. 2.—Semilogarithmic plot of the mean conjugated 17-OHCS levels in plasma after the infusion of Cortisol. Numbers in parentheses indicate the number of animals in each group. Note the high, early peak in the arterialized group, and the low, plateau-like curve for the devascularized group.

The 1 dog which was subjected to both types of anatomic rearrangement mirrored the experience of the 2 groups (Fig. 3). The disappearance curve of the free 17-OHCS was not significantly different from normal when the liver was arterialized, but when the liver was devascularized, the rate of removal was delayed. The values for the conjugated 17-OHCS rose earlier and to higher levels in the arterialized than in the normal state. After the devascularization procedure, the levels of conjugated 17-OHCS did not rise to the normal level.

Mean per cent BSP retention and S.E.M. at 5, 15, 30, and 45 minutes after injection in normal animals was 26 ± 6, 6 ± 3, 3 ± 0.5, and 1.4 ± 0.3 (Fig. 4). When plotted semilogarithmically, these values assumed a curvilinear relationship. Similar results were found in animals with arterialized livers. BSP retention in dogs with devascularized livers was consistently elevated to twice the normal level at each time period studied.

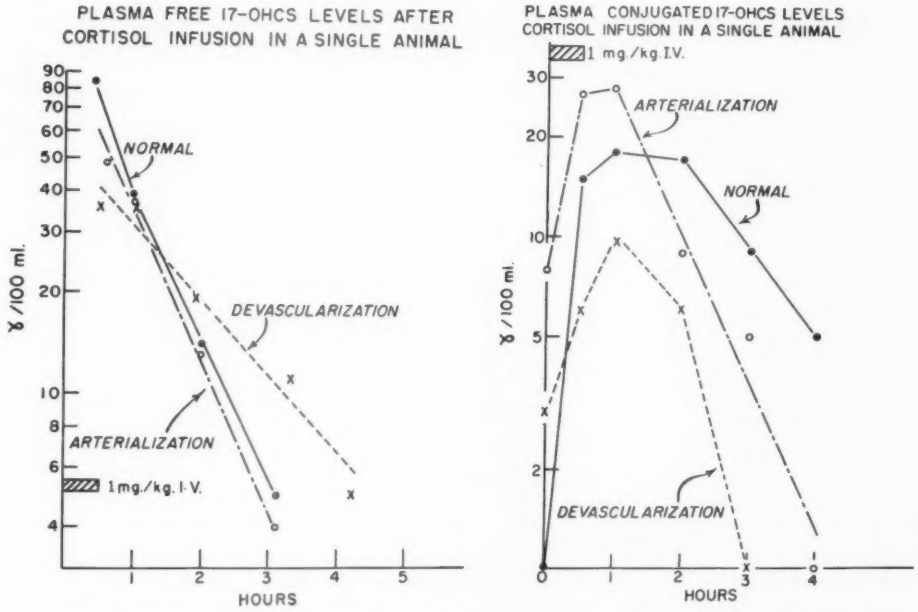

Fig. 3.—Semilogarithmic plot of the values for free and conjugated 17-OHCS in a single animal. Results were obtained in the normal state, after the liver was arterialized, and again after the liver was devascularized.

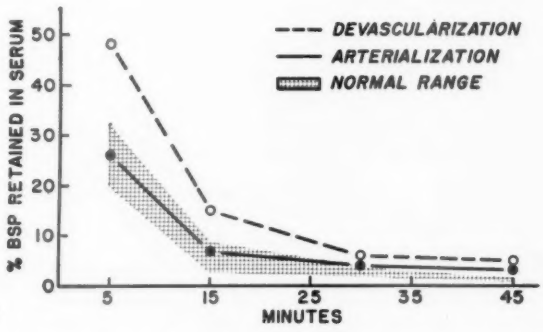

Fig. 4.—Effect of alteration of blood supply to the liver on per cent retention of BSP in serum. The dotted and solid lines indicate the mean values respectively in 4 animals with devascularization and in 3 with arterialization of the liver. The shaded area depicts the mean ± 1 standard error of the mean levels observed in 11 normal dogs.

DISCUSSION

These preliminary data suggest that surgical alteration of the blood supply to the liver of the dog, although insufficient to produce morphologic abnormalities, may alter the metabolism of Cortisol. Devascularization of the liver is associated with delayed removal of administered Cortisol from the plasma,

diminished production of conjugated 17-OHCS, and elevated BSP retention in serum. Similar observations have been made in human subjects with cirrhosis of the liver,[7] in whom it has been shown that liver blood flow is decreased.[5] In these individuals, the defect in conjugation of the 17-OHCS results from delayed formation of reduced 17-OHCS which are the substrates for glucuronide conjugation, since conjugation takes place at a normal rate if the reduced substrate is provided.[7]

In the animals with arterialization of the liver, there appears to be increased formation of conjugated 17-OHCS. This pattern was observed in humans with hyperthyroidism[1] in whom the hepatic blood flow has been reported to be normal.[10] Although hepatic blood flow was not measured in the present study, the surgical technique of hepatic arterialization is known to cause elevated hepatic blood flow.[8] Thus, the rate of conjugation for 17-OHCS in the liver may be influenced by either enzymatic or circulatory factors.

SUMMARY

Arterialization of the canine liver appears to accelerate the conjugation of 17-OHCS. In contrast, if the liver is devascularized, the rate of removal of free 17-OHCS from plasma and of conjugation of 17-OHCS are decelerated.

The technique of surgical alteration of the blood supply to the liver appears to be a useful tool for the study of hepatic physiology.

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FURTHER STUDIES OF SMALL VESSEL ANASTOMOSIS AND REPLACEMENT IN THE DOG

I. Plastic Prostheses

II. An Unidentified Host Variable Affecting Results

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(From the Naval Medical Research Institute)

PREVIOUSLY we have reported experimental studies of small vessel replacement using fresh autogenous, freeze-dried autogenous, and freeze-dried homogenous arterial grafts in the carotid artery of the dog.[2] Grafts were 10 cm. or more in length and were followed for a minimum of 1 year unless occlusion was demonstrated earlier. The following pertinent observations were made: (1) by means of end-to-end anastomoses, fresh autogenous grafts were implanted in these vessels, 5 mm. or less in outside diameter, with a reasonable degree of success (82 per cent patency); (2) freeze-dried autografts showed a significantly higher incidence of thrombosis than fresh autografts (only 36 per cent patency); (3) freeze-dried homografts appeared to function as well as the preserved autografts and were indistinguishable from them grossly and microscopically; (4) in all but 2 of the dogs with a freeze-dried autograft in 1 carotid and a freeze-dried homograft in the other, the graft successes or failures were paired. If the freeze-dried autograft in a given dog remained patent, so did the homograft (3 instances). If occlusion occurred on one side, it also occurred on the other (6 instances).

Although others[1, 3, 4, 6, 9, 10] have reported very discouraging results with the use of plastic replacements in vessels of 5 mm. or less in outside diameter, we have continued our own experiments in this field to include a study of one of these plastic prostheses. At the same time we have been interested in further testing our impression gained from the fourth observation listed above, that there is an individual variation in canine host reaction to, or acceptance of, a small vessel graft, prosthesis, or anastomosis. If this is so and does contribute to end results, it is essential to recognize the fact in planning and evaluating studies of such procedures.

I. PLASTIC PROSTHESES

Materials and Methods.—Since this was an extension of our previous study[2] and the results were to be compared, materials and methods remained unchanged. Adult mongrel dogs were used. Prostheses were 10 cm. or greater in length and

The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

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were followed for a minimum of 1 year unless occlusion was demonstrated at an earlier date. Using sodium pentobarbital anesthesia and sterile technique, we removed vessel segments and inserted the plastic replacements in end-to-end fashion. The distal anastomosis in the carotid artery was just below its thyroid branch and the proximal anastomosis was a few centimeters above the brachiocephalic artery ramification. Two continuous everting mattress sutures of No. 6-0 arterial silk were used for each anastomosis. At the conclusion of the operative procedure each dog received 1.5 million U. of penicillin and 1 Gm. of streptomycin intramuscularly.

The Helanca weave, Dacron-Teflon prosthesis (Sidebotham-Szilagyi) was selected for this experiment. We were reluctant to use the heavier crimped prostheses in these small vessels. The longitudinal stretch of the Helanca weave

TABLE I. DACRON-TEFLON PLASTIC PROSTHESES

DOG NO.	PERIOD OF FOLLOW-UP (MONTHS)	OUTSIDE DIAMETER OF GRAFT (MM.)	OUTSIDE DIAMETER OF HOST VESSEL (MM.)	LENGTH OF GRAFT (CM.)	RESULT
4410	5	5+	4.0	11.0	Patent
	5	5+	3.5	10.0	Patent
4485	6	5+	4.5	11.0	Occluded
	5	5+	4.0	11.0	Occluded
4462	13	5+	4.0	11.0	Patent
	12	5+	4.0	12.5	Patent
4568	7½	5+	4.0	11.5	Occluded
	6½	5+	4.0	12.0	Occluded
4643	12	5+	4.5	14.0	Patent
	12	5+	4.5	12.5	Patent
4585	9	5+	4.5	12.0	Patent
	8½	5+	4.5	11.0	Patent
4650	6	5+	5.0	11.0	Occluded
	5½	5+	4.5	11.4	Occluded

appeared to be of advantage and the Dacron-Teflon combination possessed characteristics[5, 7, 8, 9] which recommend it highly as a vascular replacement. The woven tubes measured 8 mm. in half circumference. This size was such that it produced a tube slightly greater in diameter than the largest vessel to be replaced.

The ends of this Helanca woven prosthesis may be prepared for suturing either by cuffing or fusing with a cautery. Both methods were used in this experiment. In each dog the prosthesis inserted in the left carotid was prepared by fusing the fibers at the ends, and that on the right was cuffed at the ends.

Fifteen plastic prostheses were inserted. One of these was lost to the experiment because of postoperative hemorrhage with the formation of a massive hematoma in the wound. Of the remaining 14, 6 (43 per cent) were occluded at the time of sacrifice (Table I). In 2 dogs patent grafts could not be followed for the full 12 months because the animals died prematurely.

The patent prostheses (Figs. 1, 2) were lined with a pseudointima which was smooth and glistening but had patchy areas of thickening, particularly at the ends. The anastomoses were wide open. In many instances the measured

circumference at the suture line was equal to or slightly greater than that of the uncontracted host vessel segment remote from the anastomosis. Longitudinal folding or pouching of the prostheses at the suture lines, best seen in Fig. 2, undoubtedly resulted from the discrepancy in size between the smaller vessel and the larger plastic tube. In addition, several patent prostheses showed wrinkling away from the suture lines, actually most marked in the central portions. This was not present in either of the 2 prostheses examined at 5 months (Fig. 1). It was observed in only 1 of the 2 prostheses removed at 9 months (Fig. 3). The central wrinkling was present and most deforming in all

Fig. 1.

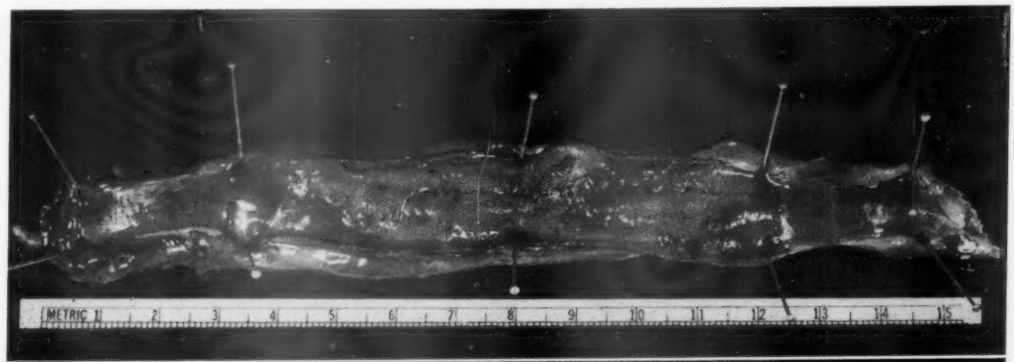

Fig. 2.

Fig. 1.—Patent prosthesis after 5 months of implantation. Note the smooth, glistening pseudointima with patchy areas of thickening most marked at the ends.

Fig. 2.—Prosthesis patent 8½ months after implantation with smooth, glistening pseudointima. Slight pouching and longitudinal wrinkling at the suture lines are probably due to the size discrepancy between the prosthesis and vessel.

of the plastic tubes which had been in situ over 1 year (Fig. 4). Mural thrombi had developed at the site of wrinkling in some instances but no significant degree of obstruction had been produced.

Grossly, the occluded prostheses presented 2 different and distinct appearances. Some were collapsed and empty with thrombosis and occlusion maximal at the proximal suture lines. These plastic tubes could be opened easily and the inner surfaces were practically free of host tissue (Fig. 5). The appearance contrasted sharply with that of the intima-lined patent grafts. In 3 instances the occluded prostheses presented as thick, completely thrombosed cords which were badly cut and torn in the attempt to open them (Fig. 6).

On microscopic examination* it could be demonstrated that the fibrils of the plastic prostheses were closely incorporated in fibrous tissue with a minimum of inflammatory cell reaction. This latter was, for the most part, in the external layer of investing host tissue and was focal rather than diffuse. The inflammatory cells were predominantly mononuclear with only occasional foreign body giant cells. The reaction was more intense around the double layer of plastic material at the cuffed ends of the prostheses than at the ends which were fused

Fig. 3.

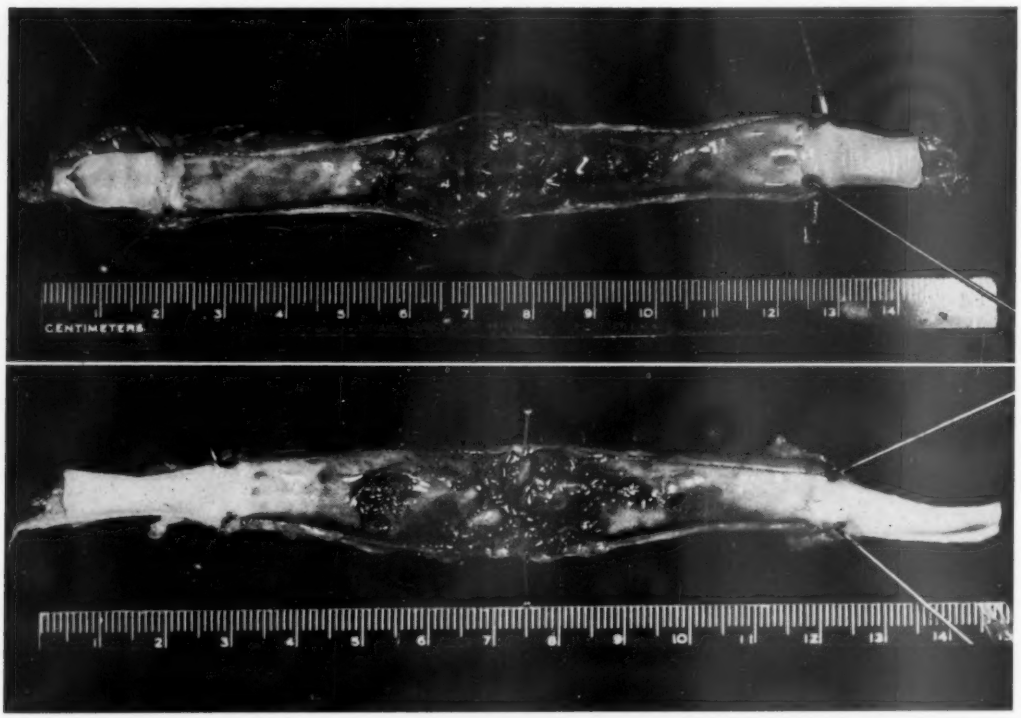

Fig. 4.

Fig. 3.—Central wrinkling and pouching in patent prosthesis 9 months after implantation. Note well-covered suture line.

Fig. 4.—Prosthesis patent after one year of implantation. Note marked central wrinking and mural thrombi. In contrast the neointima at the suture lines is quite clean and smooth.

by heat and sutured as a single layer. Localized deposits of iron-containing pigment (hemosiderin) were present in the adventitial tissues. In areas adjacent to the wrinkling in the prostheses these deposits were heavily infiltrated with phagocytes. The contrast between the minimal inflammatory reaction to the plastic material and the more marked reaction to silk was nicely demonstrated (Fig. 7).

The lining of a patent prosthesis was smoothly continuous with, and of the same quality as, the intima of the host artery at the suture line. Toward the center of the "graft," the pseudointima became generally thinner (Fig. 8). Exceptions were noted in the areas of central wrinkling where the intimal lining in the depressions was many times thicker than that over the ridges

*Formalin fixative and celloidin embedding technique was used. All sections were stained with hematoxylin and eosin. The presence of hemosiderin in the tissues was verified by differential staining using the Turnbull reaction on tissues pretreated with ammonium sulfide.

(Fig. 9), producing a smoothing effect and, presumably, a less turbulent blood flow. It was possible to demonstrate penetration of host tissue between plastic fibers, which established continuity between the internal and external layers of investing host tissue.

Discussion.—The fact that over 50 per cent of the relatively long plastic prostheses remained patent in these small vessels is rather gratifying. Although the results are far from ideal, they are better than the reported experience of others[3, 4, 9, 10] had led us to expect. Also, they represent an improvement

Fig. 5.

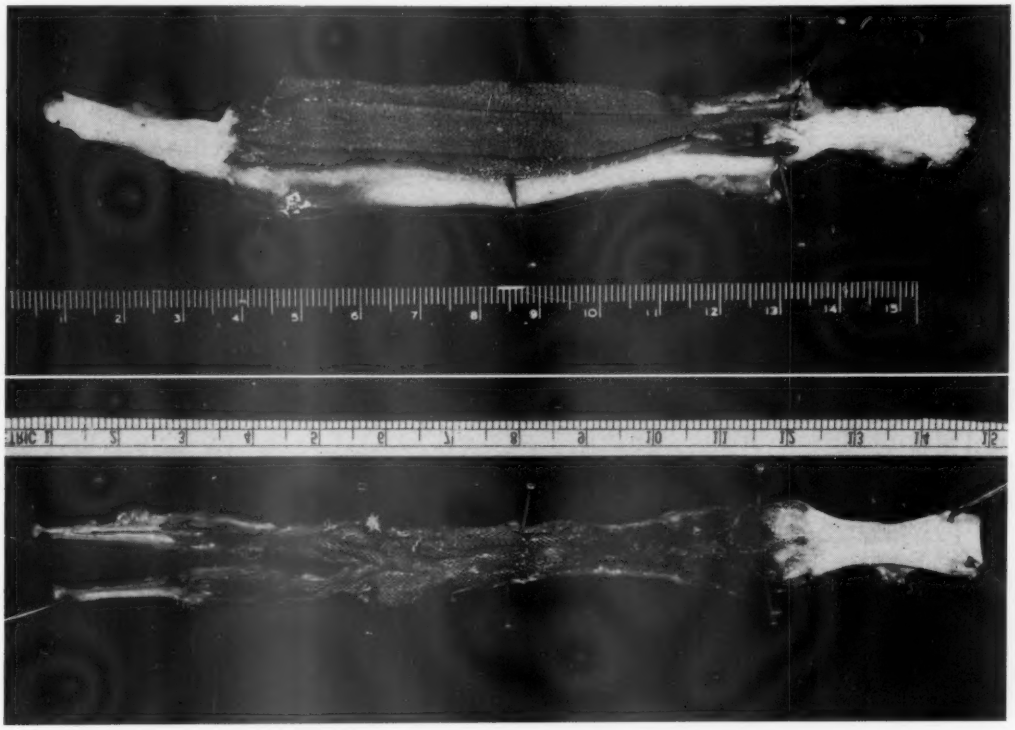

Fig. 6.

Fig. 5.—Prosthesis smoothly collapsed and empty after 6 months of implantation. No glistening pseudointima present. Note the thrombus at the proximal suture line extending for a short distance into the prosthesis.

Fig. 6.—Prosthesis thrombosed at examination 6½ months after implantation. Because of thrombi and longitudinal wrinkling, the prosthesis was shredded and torn in an attempt to open it.

over our own results with preserved autografts and homografts (57 per cent as compared to 36 per cent). Admittedly these differences are not of statistical significance since they occurred in a small series of animals.

It is postulated that the use of a prosthesis slightly greater in diameter than the host vessel contributed to its maintaining patency. The deposition of a pseudointima on the inner surface of the prosthesis produced a channel approximating that of the host vessel rather than having a narrowing effect. This applies particularly to the replacement side of the anastomosis where the wedge thrombus of healing is apt to be thickest. The fact that the oversized, slightly rigid prosthesis, particularly when cuffed, tends to prevent contraction

at the anastomosis is supported by the observation that the circumference at the suture line often equaled or exceeded that of the uncontracted host vessel.

Since all prostheses were inserted under moderate tension or stretch, it is probable that the central wrinkling was due to longitudinal contraction

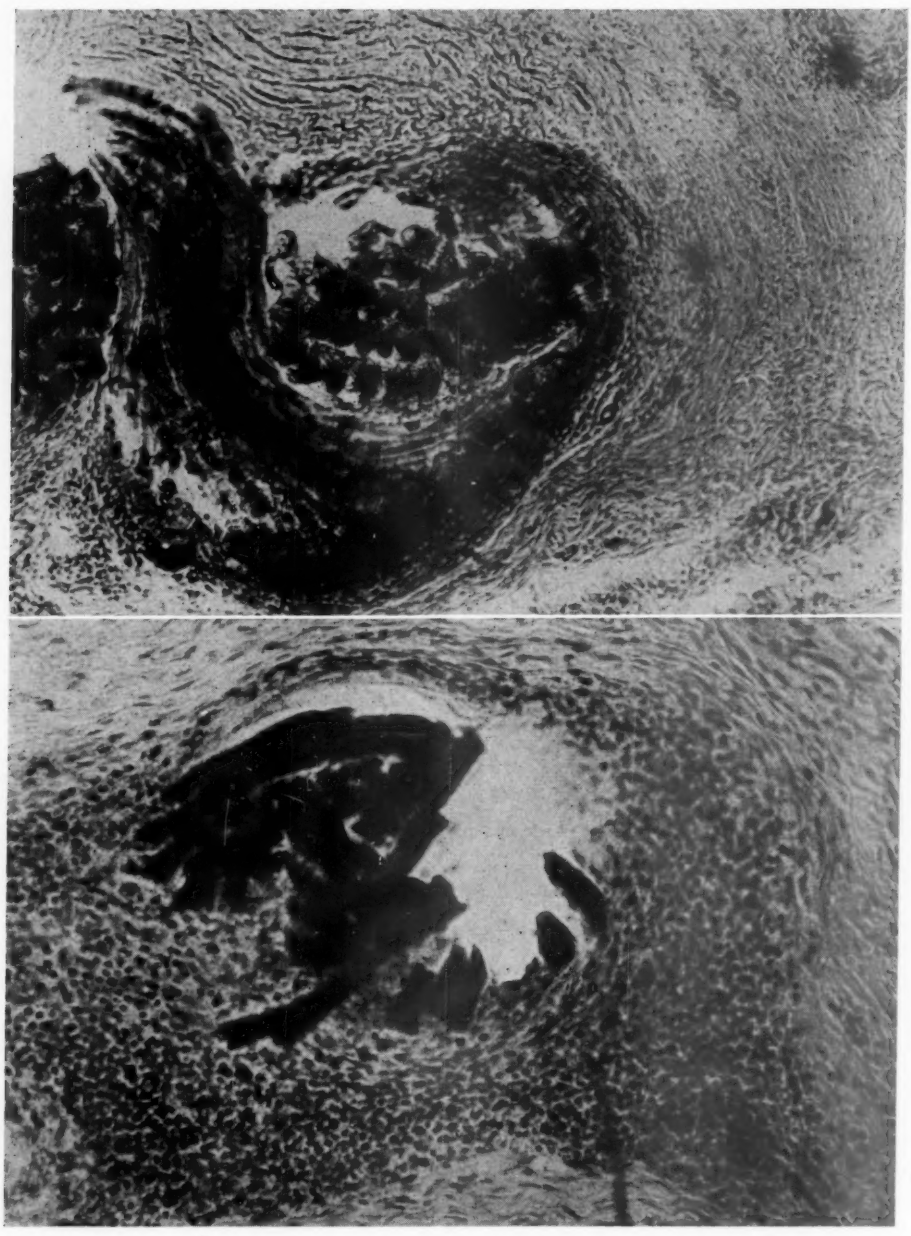

Fig. 7.—*A*, Fused end of prosthesis patent at 9 months. Note the relative absence of cellular reaction around the plastic fibrils. (Hematoxylin and eosin. ×70; reduced ⅓.) *B*, Focal cellular reaction around silk suture material used in the implantation of this same prosthesis. (Hematoxylin and eosin. ×70; reduced ⅓.)

of investing fibrous tissue rather than redundancy. This wrinkling was most marked in the prostheses that were followed the longest. If progressive beyond

a year, it could be the ultimate cause of late failure. Perhaps the use of a crimped prosthesis would have prevented or minimized this irregular and deforming wrinkling.

Short of living, autogenous vessels, the ideal or even satisfactory replacement substance for arteries of 5 mm. or less in diameter remains to be found.

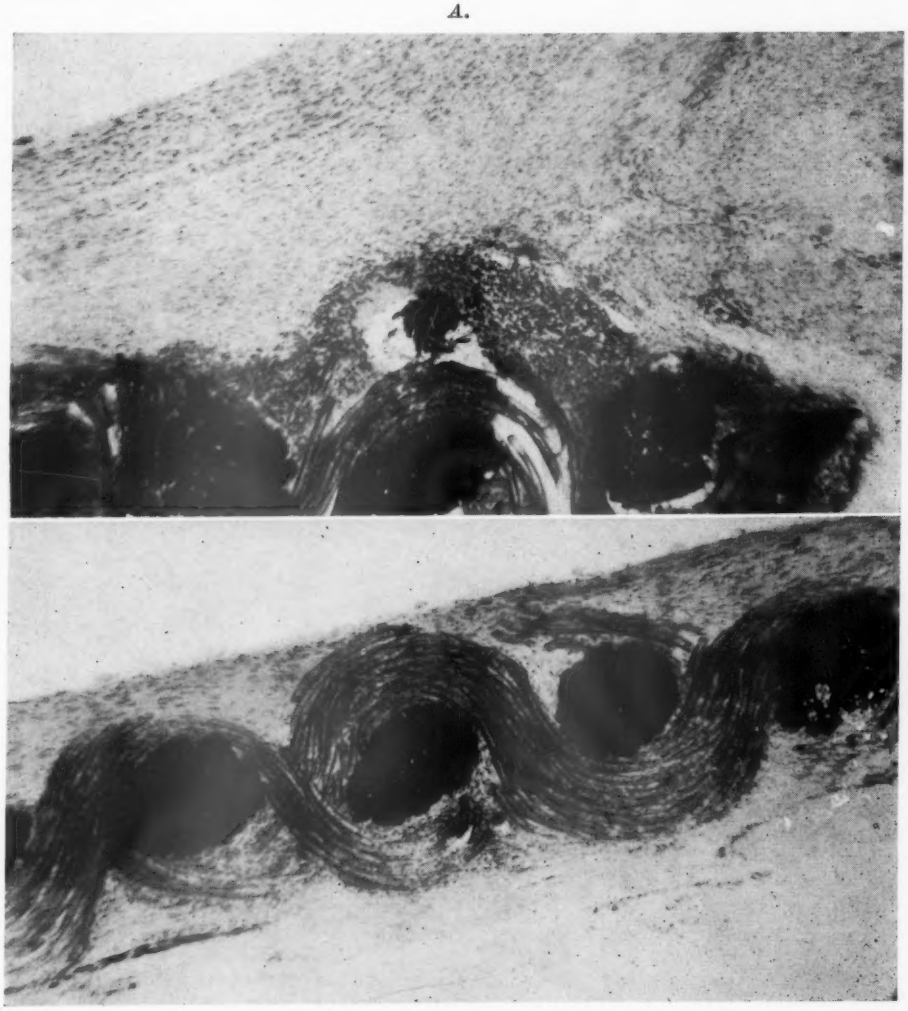

Fig. 8.—*A*, Neointima near the junction of the prosthesis with the carotid artery. Contrast this in respect to thickness with *B*, the intimal layer at the center of the same prosthesis. (Hematoxylin and eosin. ×70; reduced ⅓.)

Contrary to our preconceived ideas on the subject, this study does demonstrate that relatively long plastic prostheses can be inserted in such small vessels with some degree of success. At the least, the results should encourage further search in this direction.

II. AN UNIDENTIFIED HOST VARIABLE AFFECTING RESULTS IN SMALL VESSEL SURGERY IN THE DOG

Our previous studies[2] have suggested that there may be an individual variation in canine host reaction to, or acceptance of, vascular replacement

TABLE II. FREEZE-DRIED AUTOGRAFTS AND HOMOGRAFTS

DOG NO.	LOCATION OF GRAFT	TYPE OF GRAFT	LENGTH OF GRAFT (CM.)	OUTSIDE DIAMETER OF GRAFT (MM.)	OUTSIDE DIAMETER OF HOST VESSEL (MM.)	PERIOD OF FOLLOW-UP (MONTHS)	RESULT
2270	L. carotid	Homograft	10.0	4.0	3.0	6	Occluded
	R. carotid	Autograft	10.0	3.0	4.0	6	Occluded
2283	L. carotid	Homograft	13.0	5.0	4.0	6	Occluded
	R. carotid	Autograft	10.0	3.5	4.5	5	Occluded
2290	L. carotid	Homograft	12.5	3.0	4.0	6	Occluded
	R. carotid	Autograft	12.0	3.5	4.5	5	Patent
2279	L. carotid	Homograft	12.0	3.0	4.0	6	Occluded
	R. carotid	Autograft	12.0	3.5	3.5	12	Occluded
2432	L. carotid	Homograft	13.0	4.5	3.5	13	Patent
	R. carotid	Autograft	12.0	4.0	4.0	12	Patent
2177	L. carotid	Homograft	10.0	3.5	4.0	10	Occluded
	R. carotid	Autograft	11.0	4.0	4.5	5	Occluded
2442	L. carotid	Homograft	12.0	4.0	4.0	6	Occluded
	R. carotid	Autograft	12.0	4.0	5.0	5	Occluded
1911	L. carotid	Homograft	11.0	3.5	3.0	12	Patent
	R. carotid	Autograft	11.0	3.5	4.0	12	Occluded
2463	L. carotid	Homograft	12.0	3.5	4.5	12	Patent
	R. carotid	Autograft	11.0	3.5	4.0	12	Patent
1883	L. carotid	Homograft	10.0	3.5	5.0	6	Occluded
	R. carotid	Autograft	11.0	4.0	4.5	5	Occluded
1915	L. carotid	Homograft	11.5	4.0	4.0	12	Patent
	R. carotid	Autograft	10.5	3.5	3.5	12	Patent

substances and that this may be a factor influencing end results. The observations that led to this impression are summarized in Table II.

In all but 2 of 11 dogs the graft successes and failures were paired. This occurred in spite of the fact that the graft tissues on the 2 sides were dissimilar, one autogenous, the other homogenous. The grafts were inserted at separate operations. A careful review of the protocols revealed no satisfactory explanation for this phenomenon.

The pairing of similar results in individual dogs is even more impressive in the experiment with plastic prostheses (Table I) than in the study of autografts and homografts. In every instance, if the replacement in 1 carotid remained patent, so did that of the other. If occlusion occurred on 1 side, it also occurred on the other. Once again a careful search of protocols failed to provide an answer. Ends of the prosthesis were cuffed on the right and not on the left. Replacements on the 2 sides were made at separate operations and, in some instances, by different surgeons. Size of vessels, operating times, technical difficulties, and varying degrees of satisfaction with the procedure as recorded by the operator showed no correlation with the pairing of results.

Fig. 9.—Low power view of pseudointima filling the furrows, and thinly covering the ridges in a wrinkled portion of a prosthesis at the end of a year. (Hematoxylin and eosin. ×21; reduced ⅓.)

Finally, the data from another of our experiments on small vessel surgery were examined for evidence of this same phenomenon (Table III). In this experiment the ulnar arteries of dogs were divided and sutured. These vessels ranged in outside diameter from 2 to 2.5 mm. Once again the pairing of patencies or occlusions in individual animals was absolute.[11]

Discussion.—The data submitted would appear to support our original impression that there is an individual variation in canine host reaction to a vascular graft, prosthesis, or anastomosis, which influences end results in terms

of patency or occlusion. No leads to the factors or mechanisms involved have been found. The very existence of this unidentified but significant variable is most disturbing both in the interpretation of the results of these studies and in the planning of further experiments in this field.

There are indications that the factor or factors which promote vascular occlusion more strongly in some animals than in others operate within definite but, as yet, not clearly defined limits. There is little, if any, evidence of this phenomenon in the almost uniformly good results obtained with a variety of replacement substances in larger vessels. Also, we failed to observe pairing of the infrequent occlusions encountered in our experiments with bilateral suture and nonsuture anastomoses or with fresh autogenous grafts in the carotid arteries of dogs.[2, 11, 12] It was not until we utilized the less acceptable replacement substances, preserved grafts and plastics, in the carotid vessels or until the extremely small (2 to 2.5 mm.) peripheral vessel anastomoses were attempted that the individual variation in host reaction became apparent.

TABLE III. SMALL VESSEL ANASTOMOSES

DOG NO.	PERIOD OF FOLLOW-UP (MONTHS)	OUTSIDE DIAMETER OF VESSEL (MM.)	RESULT	
			RIGHT LEG	LEFT LEG
1	18	2.0	Patent	Patent
2	6	2.0	Patent	Patent
3	3	2.5	Occluded	Occluded
4	15	2.5	Patent	Anastomosis unsuccessful
5	6	2.5	Patent	Patent
6	9	2.0	No postmortem	
7	15	2.0	Patent	Patent
8	6	2.5	Patent	Patent
9	15	2.5	Occluded	Occluded
10	3	2.5	Patent	Patent
11	3	2.0	Occluded	Occluded
12	3	2.0	Anastomosis unsuccessful	Occluded
13	12	2.5	Patent	Patent
14	16	2.5	Patent	Patent
15	16	2.0	Patent	Patent
16	16	2.5	Patent	Patent
17	15	2.0	Anastomosis unsuccessful	Patent
18	16	2.0	Patent	Patent
19	16	2.5	Patent	Patent
20	16	2.5	Patent	Patent
21	6	2.5	Patent	Patent

It is alarming to contemplate that the results of a given experiment involving small vessel anastomoses or replacements may be predetermined by the random choice of experimental animals, that is, by the proportion of "occluders" to "nonoccluders." However, this possibility must be considered at least until there is a better understanding of the mechanisms involved.

SUMMARY

1. Experimental studies of small vessel replacements have been continued to include plastic prostheses. Long (10 cm.) Dacron-Teflon prostheses were inserted in the carotid arteries of dogs and followed for 1 year unless occlusion was demonstrated earlier.

2. The occlusion rate for the plastic replacements was less (43 per cent) than that for similarly placed freeze-dried autogenous or homogenous grafts (64 per cent).

3. It is postulated that the use of a prosthesis slightly greater in diameter than that of the host vessel contributed to its maintaining patency.

4. It was suggested by previous studies that individual variation in host reaction to, or acceptance of, a vascular graft may be a factor in determining the end result. Data are submitted from more recent experiments on small vessel replacements and anastomoses which support our original impression.

5. Although this variable has not been identified, it is essential to recognize the probability of its existence in planning and evaluating studies of small vessel anastomosis or replacement.

The authors wish to extend their appreciation to Mrs. A. B. Snodgress for the histologic preparations, and to the Corpsmen attached to the Experimental Surgery Department for the preparation and care of the experimental animals and for their assistance with the surgical procedures.

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A NEW RETRACTOR FOR INTRACARDIAC USE

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ECONOMY of time and motion is essential for the successful performance of intracardiac surgical repair of both congenital and acquired lesions. While the use of extracorporeal circulation and elective cardiac arrest permits the almost ideal surgical condition of a bloodless field which is motionless, many lesions are best repaired under conditions of uninterrupted ventricular contractions. Under either circumstance, the continuous observation of the lesion by means of reliable and unvaried retraction of the walls of the heart is desirable.

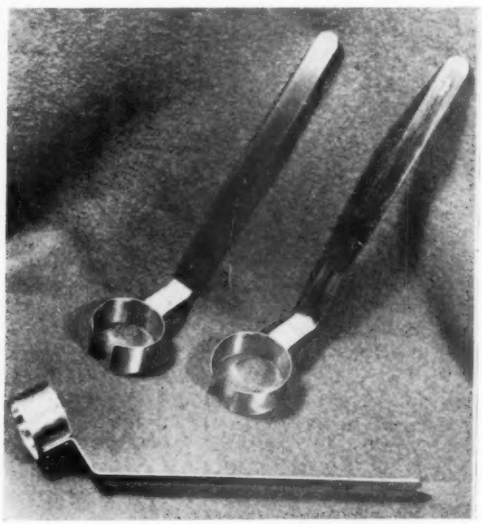

Fig. 1.—Three sizes of the retractor.

The retractors illustrated in the accompanying photograph have been found to be useful in exposing atrial and ventricular lesions under direct vision repair. They are constructed of malleable stainless steel, which allows the relationships of the various parts to be adjusted. Under some conditions they are self-retaining in the heart, and at most require stabilization by only one hand. Intracardiac catheters from the venae cavae can be retracted by the blades, which are deep enough to retain them. The offset handle not only stabilizes the depth of the retractor at the heart wall, but also permits the handle to remain out of the immediate operative field. Three sizes have been made, which vary from 1½ to 2 inches in diameter. The open side of the retractor permits it to be removed from the heart while sutures into the interior of the heart remain in place.

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Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

VARIOUS INTESTINAL SEGMENTS UTILIZED FOR BLADDER ENLARGEMENT IN PEDIATRIC PATIENTS, WITH REFERENCE TO THE MANAGEMENT OF EXSTROPHY

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THIS report describes the use of 3 different intestinal segments in cystoplasty. In this instance they were employed to enlarge the flat, rudimentary bladder found in exstrophy. Principles regarding ease of approximation to the bladder, integrity of anastomosis, distensibility, etc., would apply to the use of intestine in any pediatric condition requiring vesical enlargement.

The use of isolated intestinal segments to form conduits or reservoirs in the urinary tract has been extensively described. This includes the employment of the terminal ileum as a bladder substitute, as a ureteral replacement, and for enlargement of bladder capacity. The colon also has been used but less extensively.[9]

In the present discussion no attempt will be made to review the history of the operative repair of exstrophy. For 2 decades bilateral ureterosigmoidostomy with cystectomy has been widely accepted as the indicated surgical management in this condition. Only recently have the late effects of this procedure upon renal function become generally known[2, 4] and the poor prognosis for adult life become well established. This has led to a revival of attempts to retain the rudimentary bladder and form an anterior wall[6, 8] or to retain the trigone and implant this intact segment of the bladder containing the ureterovesical junction into the defunctionalized colon.[1] Reconstructive procedures, described by numerous other surgeons, have been summarized in a recent monograph by Sorrentino.[7]

In some of the patients in this series, intestinal segments were used to form an outflow tract from the reconstructed bladder to the perineum and a 5-year study of this group is now in progress. Other operative approaches to the problem of exstrophy are now being evaluated in this institution, and the general management of this problem will be reviewed subsequently. Although in occasional cases of exstrophy a large mucosal surface is exhibited, there is a greatly contracted surface area in the majority, and enlargement seems de-

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sirable prior to any type of reconstruction. The present experience in bladder enlargement (13 patients) is briefly described for the information of surgeons interested in the use of intestinal segments as urinary conduits or reservoirs.

METHODS

The Cecum Used as an Isolated Intestinal Segment.—Two females with exstrophy, age 3 years and 4 years, in whom anterior cystoplasty (attempted elsewhere) had been unsuccessful, underwent a procedure enlarging the bladder with cecal wall. A wide cuff of cecum surrounding the appendiceal base was resected and the cecum closed. This segment, with mesentery intact, was then swung into the pelvis where the cecal flap, which was approximately 4 cm. in diameter, was introduced into the posterior vesical wall in the midline at a point immediately superior to the trigone. Anastomosis was formed with internal (bladder) absorbable and external nonabsorbable interrupted sutures. The entire segment, with the exception of the mesentery, could be placed in an extraperitoneal plane. Both patients subsequently underwent anterior plastic procedures designed to secure continence. No further bladder enlargement was necessary.

In the initial operation performed upon these patients following the bladder reconstruction, the vermiform appendix was brought down through the right broad ligament and thence to the perineum in a plane anterior to the rectum.* The appendiceal tip was passed through the superficial anal sphincter, opened, and sutured to perineal skin. Although in 1 patient adequate bladder drainage through the appendix was maintained for more than 1 year, both patients ultimately developed stenosis of the lumen. Anterior vesical drainage, followed by plastic repair, was required. A mild unilateral (left) hydronephrosis was observed in both of these patients postoperatively, without specific explanation except for the operative procedure.

Ileum Used as an Isolated Intestinal Segment.—In 3 children, 2 to 4 years of age, ileum was used to enlarge the bladder capacity in exstrophy. An intestinal segment lying 6 to 20 cm. proximal to the ileocecal valve, and 10 to 15 cm. in length was isolated in each instance and brought to the anterosuperior aspect of the rudimentary bladder. The ileal mesentery passed along the right side of the pelvis where it was secured. In 2 of the children the intestinal segment was opened along the antimesenteric border. This formed a large sheet of ileal wall which was introduced into the structure of the bladder in the midline both superiorly and anteriorly. Here it was secured with interrupted and continuous absorbable sutures. When in place, the ileal segment lay entirely in an extraperitoneal space, except for the mesentery. Subsequent closure of the anterior aspect of the bladder wall, including both the original vesical tissues and the introduced ileal wall, was accomplished. The anterior abdominal wall was closed in layers with formation of an outflow tract utilizing a pedicle graft of bladder mucosa as devised by one of the authors (T. P.).

*The first operation of this type was performed on March 31, 1955.

In the third child in whom ileum was employed the isolated segment was not opened following resection. The proximal end of the segment was anastomosed to the fundus of the bladder, and the distal end brought to the perineum in a manner similar to that described in the previous section. The perineal portion of this ileal segment was excised 2 years following the initial procedure because it had dilated excessively, forming a large bladder diverticulum. The use of the remaining portion of this segment was successful in enlarging bladder capacity to normal volume, and anterior bladder closure with a degree of continence has been achieved (Fig. 1).

Sigmoid Colon Used as an Isolated Intestinal Segment.—In 8 patients with exstrophy an isolated segment of the sigmoid colon was employed for bladder enlargement.* Some form of anterior bladder reconstruction had been attempted elsewhere in 5 of these children. In 1 case this had included 6 operative procedures, and in a second, 2 operative procedures. The age range was from 2.5 to 7.5 years. Four were male and 4 female. All had normal or mildly altered preoperative intravenous pyelograms, normal blood urea nitrogen determinations, and varying degrees of urinary tract infection as evidenced by pyuria and hematuria.

Fig. 1.—Cystogram of a 5-year-old female with exstrophy performed 2 years following enlargement of the rudimentary bladder with an isolated segment of ileum.

A segment of sigmoid colon, approximately 10 cm. in length and lying immediately proximal to the pelvic peritoneal reflection was resected with preservation of the mesocolon. Bowel continuity was re-established by an end-to-end anastomosis. A vertical incision was then made in the midline of the posterior vesical wall. This extended for 3 to 4 cm. superiorly from the trigone. The isolated colon segment was then brought through the reflected parietal peritoneum covering the bladder, so that only the superior surface of its mesentery

*This should not be confused with the Gersuny[3] or Heitz-Boyer and Hovelacque[5] operations for exstrophy in which the fecal stream is diverted. The first operation of this type was performed on Dec. 21, 1955.

remained within the peritoneum. The proximal end of this segment was passed through the fenestration previously made in the bladder wall. Here it was secured internally by interrupted absorbable sutures uniting the mucosal layers of colon and bladder. Externally interrupted nonabsorbable sutures were used to approximate the colon serosa and the adventitial surface of the bladder. In 6 patients the function of this colon segment has consisted solely of bladder enlargement, and subsequent anterior, plastic reconstruction to secure continence has been performed or is contemplated.

In the original procedure in these 8 cases a passage through the pelvic floor was formed immediately anterior to the rectum. In the male this passed posterior to the trigone (previously freed), the prostatic area, and the transverse perineal musculature. In the female it transversed the base of the left broad ligament and lay immediately posterior to the vagina. A perineal incision was then made anterior to the anus, the superficial sphincter fibers retracted anteriorly, and the distal end of the colon segment brought to the skin incision. The anterior bladder wall was closed and the anterior fascia, skin, and subcutaneous tissues were mobilized by means of lateral incisions and were closed with wire sutures. The genital tract in the males was preserved for further reconstruction.

Fig. 2.—Cystogram in a 4-year-old male with exstrophy, performed 2 years following bladder enlargement with an isolated sigmoid colon segment.

In 2 patients, the original anterior bladder closure remained intact, and total bladder drainage has been maintained through the colon segment for over 2 years. They have a large vesical capacity (Fig. 2) and void at will in a full, strong stream that completely empties the bladder. They are never found to "wet," i.e., they do not "dribble" or "overflow." On the other hand, under conditions of stress, they may experience a sudden, involuntary, complete emptying of the bladder.

COMPLICATIONS

There was no operative or postoperative mortality directly attributable to these procedures. A relatively benign immediate postoperative course was noted

in all patients, with the exception of 1 infant who, following reconstruction with sigmoid colon, developed ileoileal intussusception requiring laparotomy and reduction. Prolonged ileus was noted in 2 additional cases. The genitourinary complications included anterior urinary fistulas (8), ascending infection (2), and the development of a vesical calculus* 18 months following bladder reconstruction.

INTRAVENOUS PYELOGRAMS AND OTHER STUDIES

Preoperative intravenous pyelograms performed upon these patients showed various degrees of mild pyelectasia, as usually found in exstrophy. Pyelograms were performed upon 5 patients at 3 to 6 months following bladder enlargement, and upon 7 patients 12 to 18 months postoperatively. In 3 of these there was a recognizable alteration from preoperative studies. These patients had a minimal unilateral caliectasis noted 1 year following the procedure. Serum electrolyte concentrations have not been altered in any of these patients. Of interest are the 2 patients in whom urinary drainage has been maintained entirely through the perineal (intestinal) tract for over 2 years. Normal pyelograms were taken 18 months following operation in the first and 6 and 12 months postoperatively in the second. In both, nonprotein nitrogen, serum sodium, serum potassium, serum chloride, and serum carbon dioxide determinations were within normal limits 18 and 24 months following bladder reconstruction.

DISCUSSION

All of the 3 types of intestinal segment employed were satisfactory in enlarging bladder capacity in children.

Sigmoid colon was most frequently utilized (8 cases). Its proximity to the posterior aspect of the bladder makes it possible to place the entire segment, often including the mesocolon, in an extraperitoneal plane, eliminating the possibility of intraperitoneal complications. Ileal segments were more readily approximated to the anterosuperior aspect of the bladder. The ileal mesentery must pass across the pelvic inlet, but may be attached laterally to prevent its acting as a source of intestinal obstruction. One ileal segment proved too distensible and acted as a diverticulum. Cecum also formed a satisfactory vesical wall, but was somewhat more difficult to mobilize. Except for the presence of the appendiceal diverticulum, which was unsuccessfully employed as a conduit here, it has no advantages over the other intestinal segments. Mucus accumulation in the bladder occurred with all types, but seemed to decrease to insignificant proportions as urine outflow increased. A benign course was usual following these procedures regardless of the intestinal segment employed. The hope that urinary control might be achieved by passing an isolated intestinal segment beneath the anterior portion of the superficial sphincter, a procedure originally described by one of the authors (T. P.), was also entertained in some of these cases.

The unusual type of infrequent incontinence described in the previous section has been produced in 2 of these patients. In the remainder the use of

*The simple removal of this calculus was followed by fatal aspiration pneumonia which caused the only death in the series.

the conduit has been abandoned because of stricture, and anterior plastic closure has been employed. Continence in those patients with combined anterior plastic closure and bladder enlargement with intestine may be described as follows: (a) one is regarded by the parents as continent, with very infrequent episodes of "stress incontinence," (b) two are incontinent, and (c) seven are either too immature for evaluation (less than 3½ years) or their procedure has not been completed.

It has been found possible to enlarge the atrophic bladder in cases of exstrophy and to form an intestinal conduit from it without apparent renal damage or significant systemic injury. Optimistically, one might predict that such enlarged bladders may be ultimately made continent by anterior plastic procedures, with or without the use of additional intestinal segments. There is nothing inherent in any of the procedures performed in this series which would complicate an eventual retreat to any of the current standard operations for exstrophy.

SUMMARY

Three different isolated intestinal segments, sigmoid colon, ileum, and cecum, have been successfully employed to enlarge bladder capacity in 13 pediatric patients. Sigmoid colon (8 cases) may be readily approximated to the posterior bladder wall. These segments, including the mesocolon, may be placed completely in an extraperitoneal plane. Ileum (3 cases) is more readily introduced into the anterior and superior vesical wall. Cecum (2 cases) is also satisfactory for bladder enlargement but is less readily mobilized. Intravesical mucus accumulation was not a significant problem in these patients. Complications (both with the use of sigmoid colon) included: (a) postoperative ileoileal intussusception, and (b) the development of a bladder calculus. A secondary aim in many of these patients was to extend the intestinal segment to form an outflow tract to the perineum. Success in this regard has been limited and will be subsequently reviewed.

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SOLITARY LIVER ABSCESS IN A NEWBORN

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IN his monograph on the umbilicus and its diseases (1916) Cullen[6] mentions the severe epidemics of umbilical infection in the past and the effect which the introduction of aseptic methods has had in their prevention. He says: "It is clearly evident that even at the present time an insidious infection occasionally exists and that it may lead to the child's death, before the original focus of infection has ever been suspected. In every instance of illness in a newborn infant it should always be the rule to inspect and, if necessary, reinspect the navel."

These words are still valid, even in our antibiotic era.

We have recently seen a serious complication in connection with umbilical infection.

CASE REPORT

The patient was a boy, 5 days old when admitted in the Pediatric Department. The mother was 21 years old, the patient being her fourth child. She was well throughout this pregnancy and was delivered of the baby at home smoothly at term on June 20. The umbilical cord was cut with a razor blade by a neighbor, who helped during the delivery. Shortly after this both mother and child were transferred, *societatis causa*, to the maternity ward in Rigshospitalet. During the first 3 days after admission nothing abnormal was noticed in the baby and there were no signs of umbilical reaction. On the fourth day the child was rather limp in the evening. The next morning temperature reached 39.1° C. and the child began to vomit, after which he was transferred to the Pediatric Department under observation for peritonitis. The abdomen was distended, meteoristic, and tender. The umbilicus was a little crusted and moist but there was no local inflammation. Unfortunately a bacteriologic swab from the navel was not taken. The condition was regarded as peritonitis originating from umbilical infection and treatment with sodium penicillin (150,000 U. twice a day) and duostreptomycin (0.05 Gm. twice a day) was instituted. In the evening the temperature was 38.9° C. The next day the temperature was normal but now nuchal rigidity was observed and a lumbar puncture was performed. The spinal fluid contained 356/3 mononuclear cell per cubic millimeter, but there was no bacterial growth. Dosage of penicillin was increased to 500,000 U. twice a day and additionally tetracycline 0.025 Gm. four times a day was administered. During the following days the general condition was quite good and the temperature was normal. The baby still whimpered, however, and appeared to be in pain and the abdomen was still distended. A plain film taken on June 27 showed inflated stomach, small bowel, and several fluid levels. Bowel function was normal and there was no vomiting. From June 27 to 29 redness and swelling of the second right toe were noticed. On June 29, a round cystic mass was palpable in the epigastrium, increasing in the following days. Roentgenograms of the stomach, colon, and urinary tract showed no abnormalities. Streptomycin was discontinued on June 29, tetracycline on July 2, and penicillin on July 3. The temperature stayed within a normal range, but the epigastric mass mentioned above increased and operation was decided upon.

Jaundice had never been observed.

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Operation was carried out July 8 when the baby was 18 days old. The abdominal wall was found to be edematous and directly beneath it a 2½ by 1½ inch large cavity was entered which contained thick, yellow pus. Biopsy of the cavity wall was taken and the abscess was drained. A swab from the abscess grew colibacteria. Micropsy proved the wall to consist of liver. Histologic diagnosis was abscessus hepatis. The postoperative course was smooth. The cavity of the abscess granulated quickly and when the patient left the hopital on July 24 the lesion was nearly closed.

The baby continues to thrive.

Epicrisis.—The patient was a 5-day-old boy, whose umbilical cord was cut shortly after birth without sterile precautions. He was admitted with fever, vomiting, and abdominal distention. Signs of septicemia and peritonitis were present, but under antibiotic therapy the child improved. Peritoneal inflammation persisted, and gradually an epigastric mass became palpable. At operation a *B. coli* abscess in the left lobe of the liver was drained and the child recovered.

DISCUSSION

Pyogenic hepatic infection resulting in an abscess is usually considered to develop in 3 ways: (1) through the portal vein, (2) through the hepatic artery, or (3) through the biliary ducts. Infection of the portal vein, the so-called pyelophlebitis, originates from a primary infection in one of the organs drained by the portal vein, most often appendicitis. In the newborn there is a special risk of infection along this route, because a navel infection is able to reach the portal vein through the umbilical vein and thus the liver. About 5 days after birth the umbilical vein usually is obliterated completely. This process may be delayed in case of inflammation. The liver can also be infected along the small lymph vessels which run along the umbilical vein. With the exception of the very mild cases of umbilical granuloma, umbilical inflammation is very rare today. Recent examinations show, however, that bacteria very often are harbored in the navel of the newborn, particularly in institutions. Edmunds and associates[7] were thus able to grow staphylococci from the umbilicus on the eighth day after birth in 40 per cent of the babies in 3 different maternity wards in Edinburgh, but only in 8.6 per cent of babies born at home. The percentage of penicillin-resistant strains was considerably higher in children born in hospitals than in those born at home. In 1956 Boissard and Eton[3] and Kwantes and James [14] described epidemics of puerperal infection caused by hemolytical streptococci in 2 maternity wards. This was because a large number of the infants harbored hemolytic streptococci in the navel and it was assumed that the infection had been carried from the personnel by way of the children's navels to the mothers. On examination of 211 cases Fairchild and associates[8] found staphylococci in 210 cases in at least 1 swab from the umbilicus during the first six days of life.

In all these publications there were remarkably few children with clinical manifestations of umbilical inflammation. Consequently it must be presumed that other factors (trauma, low resistance) must contribute before clinically manifest infection appears. In this connection, however, one must bear in mind that disastrous infection can emerge from the umbilicus, even though local inflammatory signs are scarce. This circumstance is emphasized by Friedländer,[9] Chamberlain,[5] and Morrison,[16] among others, and is also illustrated by several

of the previously described cases of liver abscess (Kutsunai,[13] and Beaven[2]). In our case, although no significant umbilical inflammation was noticed, the infection most likely was spread through the navel.

From the umbilicus the infection spreads partly hematogenously as sepsis, partly by direct migration to the peritoneum, and finally, as mentioned above, through the umbilical vein or its perivenous lymph vessels to the liver. The fact that the liver can be infected through the umbilical vein in cases of umbilical infection is evident from examinations made by Morrison.[16] In 9 children, aged 9 to 28 days, all suffering from umbilical inflammation, he found interstitial hepatitis consisting of leukocytic infiltration along the ramification of the portal vein.

In neonatal sepsis the umbilicus in many cases quite certainly is the source of infection, although this may not be recognized because of the absence of local affection. Hagelsteen[10] found that in 20 cases of neonatal sepsis the infection originated from the umibilicus in 16 cases.

In the Pediatric Department, Rigshospitalet, Copenhagen, 15 children (3 months of age or younger) have been admitted with neonatal sepsis during the last 10 years, and in only 3 of these cases has umbilical infection been recorded.

In his survey of the source of peritonitis in the newborn, Rickham[19] does not mention umbilical infection. A perusal of our material of peritonitis in early infancy (18 cases during the last 10 years) has not revealed any instance of the infection arising from the umbilicus. Nevertheless such cases have been reported (Chamberlain,[5] Holve,[12] and Beaven[2]) and it should be considered in cases of peritonitis in the newborn.

In pediatric texts (Nelson, Holt and McIntosh) it is stated that multiple abscesses of the liver are seen in the newborn as a complication of umbilical infection. These abscesses, however, are small and usually not recognized before autopsy. Holt and McIntosh[11] write that solitary abscess of the liver is very rare in early infancy.

Of the above-mentioned 15 children with neonatal spesis in the Rigshospitalet, 10 died. On autopsy multiple liver abscesses were found in 3 cases. None of these had shown any signs of umbilical reaction. Multiple small abscesses of the liver as a stage in the neonatal sepsis can therefore not be so very uncommon. However, large, localized abscesses seem to be more rare. In a review we have been able to find very few cases, in all of which the author assumes that the infection issued from the umbilicus. Even when umbilical infection was more common than it is today instances of liver abscess seem to have been scarce. In his thesis on umbilical infection, Audion[1] does not mention abscess of the liver. In some of the cases he states that the liver showed signs of inflammation, but nothing is mentioned about the development of abscess. This probably means that the children died before the abscess had developed. In another article about umbilical infection[4] only small septicemic abscesses of the liver are described.

In 1906 Legrand[15] reviewed the literature concerning abscesses of the liver in infancy, and he found 112 cases. One occurred in a 3-month-old child, the youngest of the group. This case was published in 1889 by Rusche.[20] The

etiology was dubious, but the author states that the infection entered through the navel. This case is especially remarkable in view of the fact that the patient survived after incision of 3 large abscesses of the liver, 2 in the left lobe and 1 in the right lobe.

Kutsunai,[13] in 1936, published a report of solitary liver abscesses in two 6-week-old infants with umbilical inflammation. The diagnosis was made on autopsy. Kutsunai found 7 similar cases in the literature out of 145 reported cases of liver abscesses in children.

We have been able to find 2 additional cases.

Pouyanne and Martin[17] described a case of an 8-day-old infant who developed umbilical abscess, signs of septicemia, and enlarged liver. On puncture in several places in the liver pus discharged, and it was concluded that there were several abscesses. The baby recovered after treatment with sulfonamides, penicillin, and aureomycin.

The other case is reported by Beaven.[2] He mentions 5 cases of staphylococcal peritonitis in infancy. In one of these cases autopsy showed a solitary liver abscess with the infection arising from the umbilicus. No clinical signs of umbilical reaction had been noticed in life.

CONCLUSION

In cases of peritonitis or sepsis in the newborn attention must be drawn to the possibility of an umbilical infection. Umbilical swabs should be cultured, and it must be realized that the navel can be the source of disastrous general infection, even when local signs of inflammation are scarce or perhaps totally absent. In cases of peritonitis, where there is reason to believe that the infection has originated in the umbilicus, it is our opinion that primarily medical treatment should be instituted, first of all as an intense antibiotic treatment, possibly guided by determination of bacterial resistance in umbilical swabs. Only when signs of localization are encountered does the question of operative treatment arise, since abscess of the liver would then be a possibility.

There seem to be 2 kinds of liver abscesses in newborn babies with different courses and different morphology. One runs a rather fulminant course, being part of a universal sepsis and on autopsy multiple, small abscesses in the liver are found. In such cases the focus of the infection is not necessarily in the navel, although this very often happens. The other type runs a subacute, less violent course and one or perhaps a few larger, localized liver abscesses are found. In the latter the bacteria apparently always originate from the umbilicus. The protracted course enables diagnosis in vivo with the possibility of successful surgical treatment.

SUMMARY

A case of solitary liver abscess in a newborn infant is reported, probably issuing from umbilical infection. In the discussion an account is given of the examinations which shows that during the neonatal period the navel very often harbors bacteria. Despite this, clinical infection occurs very seldom, but it is

emphasized that the umbilicus can give rise to disastrous general infection even when local signs of inflammation are scarce or entirely absent. A short survey of the literature regarding abscesses of the liver in the newborn is rendered, from which it appears that only 11 cases of localized liver abscesses in the newborn, all derived from umbilical infection, have been reported until this time.

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NEONATAL GASTRIC PERFORATION CAUSED BY CONGENITAL DEFECTS OF THE GASTRIC MUSCULATURE

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THE medical literature contains reports of more than 80 cases of neonatal gastric rupture. The etiologic factors which have been implicated are summarized in Table I. Herbut,[7] in 1943, was the first to call attention to congenital absence of the muscular coat of the stomach as a cause of such gastric perforation. Since his report only 13 other cases have been described in which there was histologic confirmation of a defect in the muscular layer of the wall of the stomach (Table II).

Table I. Causes of Gastric Perforation in the Newborn

1. Acute or chronic peptic ulceration[1]
2. Absence of muscle[7]
3. Ruptured diverticulum[3]
4. Gastric intubation[15]
5. Distal gastrointestinal obstruction[14]
6. Abdominal trauma at birth[5]
7. Cerebral anoxia[8]
8. Ulceration due to intracranial hemorrhage[4]
9. Overwhelming septicemia with gastric necrosis and ulceration[14]
10. Idiopathic

While serving as Chief of Surgical Services at the 5060th USAF Hospital, one of us (JHA) had occasion to treat an infant with this condition (Case 1). Two other cases have been seen at the Jefferson Medical College Hospital since the 1 previously reported by Herbut. These 3 cases are the basis for this report.

CASE REPORTS

Case 1.—A premature white male was delivered in the thirty-fourth week of gestation by emergency cesarean section for premature separation of the placenta. Birth weight was 1,680 grams. The mother was 24 years of age and had had no previous pregnancies. The serologic test for syphilis was negative and the blood was Rh positive. Oral feeding of the infant was begun on the second day. The child remained well until the afternoon of the third day when respiratory distress with cyanosis was first noticed. Subsequently the infant vomited once and abdominal distention appeared. Roentgenograms taken 4 hours after the onset of symptoms showed a massive pneumoperitoneum with fluid in the peritoneal space (Fig. 1). A nasogastric tube was inserted, the infant was taken to the operating room, and a laparotomy was performed. There was cloudy, yellow-brown fluid with flecks of curdled milk in the peritoneal space. Cultures of this fluid yielded growth of *Herellea vaginicola*. A large part of the anterior gastric wall was necrotic and there was an oval perforation 4 cm. in diameter near the greater curvature. A biopsy was made of the

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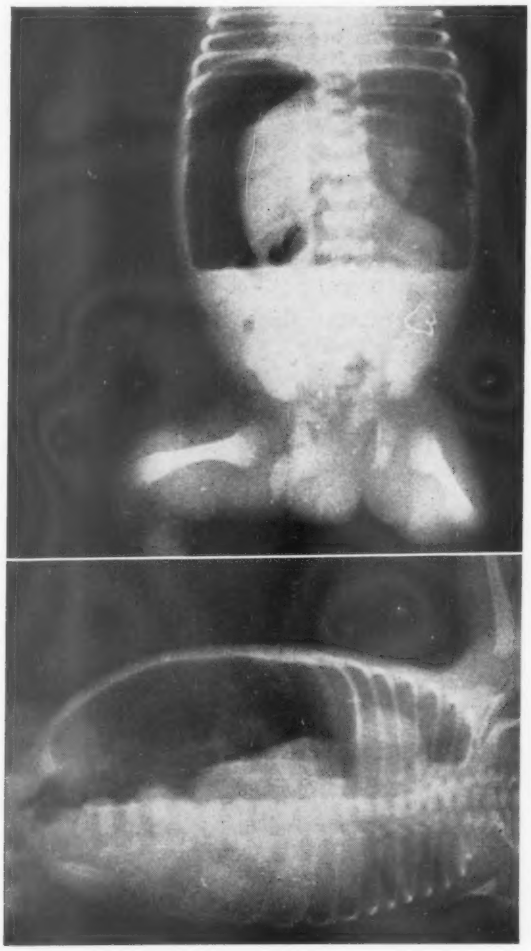
margins of the perforation, necrotic gastric wall was removed, and the defect closed in 2 layers. Fluids and blood were administered intravenously during and after operation. The infant's condition was poor postoperatively. Despite nasogastric suction the abdomen remained distended, peristalsis did not return, and he died 48 hours after operation.

The surgical specimen submitted measured 3 cm. in longest dimension. The mucosa was necrotic and there were intense edema and acute inflammation of the submucosa. The muscularis mucosa was present but none of the sections revealed any muscular coat in the wall. Neutrophils, fibrin, and clumps of bacteria coated the outer surface of the

A.



B.

Fig. 1.—*A*, Erect and *B*, lateral recumbent roentgenograms showing massive pneumoperitoneum and an air-fluid level in Case 1.

gastric wall (Fig. 2). At the time of postmortem examination the abdomen was moderately dilated and there was little fluid in the peritoneal cavity, but diffuse peritonitis was present. Sections of the stomach taken from the area of perforation were similar to those of the biopsy specimen, but those from other regions of the stomach were normal microscopically. No other abnormalities were noted.

CASE 2.—A 2,010-gram Negro girl was delivered spontaneously in the thirty-seventh week of a normal pregnancy. The child remained well until the third day when respiratory distress with cyanosis and abdominal distention were first noticed. She vomited bile-stained fluid several times. Roentgenograms revealed pneumoperitoneum. Ten hours following

TABLE II. SUMMARY OF HISTOLOGICALLY CONFIRMED CASES

	SEX AND RACE	AGE AT ONSET (DAYS)	AGE AT DEATH (DAYS)	CLINICAL MANIFESTATIONS	INTUBATION PRIOR TO ONSET	SURGICAL TREATMENT	LOCATION OF PERFORATION	ASSOCIATED DISORDERS
Herbut, 1943	M N	4	5	Respiratory distress, abdominal distention, vomiting	No	No	Midportion of greater curvature	None*
Potter, 1952	?	?	?	?	?	?	?	?
Braunstein, 1954	F N	10 (premature)	11	Cyanosis, respiratory distress, abdominal distention	Yes	No	Greater curvature, near the cardia	None
	F N	2	4	Cyanosis, respiratory distress, melena, hematemesis	No	No	Near the cardia	None
	M N	3 (premature)	3	Cyanosis, respiratory distress	No	No	Greater curvature, near the cardia	None
	M N	9	9	Cyanosis, dyspnea, abdominal distention	Yes	No	Midportion, near greater curvature	Congenital syphilis
Griffin and Griffin, 1954	M C	3	7	Cyanosis, vomiting, toxemia	No	No	Fundus	None
Vargas et al., 1954	M ?	6	6	Not specified	No	No	Greater curvature, near fundus	None
	M ?	7	16	Not specified	Yes	Yes	Anterior wall, near greater curvature	Bilateral hydronephrosis, intracranial hemorrhage
MacGillivray et al., 1956	M ?	2	4	Pallor, respiratory distress, abdominal distention, subcutaneous emphysema	Yes	Yes	Anterior wall, from greater curvature to lower esophagus	Hypoplastic kidneys, hydroureter with strictures at ureteropelvic junctions and congenital valve of urethra

Musser, 1956	F	C	At birth	13 hrs.	Respiratory distress	No	No	Fundus	Hypoplastic kidney, diaphragmatic hernia
Meyer, 1957	M	N	3 (premature)	5	Abdominal distention, lethargy	No	Yes	Greater curvature, anteriorly	None
	M	C	4	4	Cyanosis and abdominal distention following surgical correction of ruptured omphalocele	No	No	Greater curvature	Omphalocele
McCormick, 1959	M	N	4 (premature)	4	Respiratory distress	Yes	Yes	Greater curvature	None
Case 1	M	C	3 (premature)	5	Respiratory distress, abdominal distention, cyanosis	No	Yes	Greater curvature, anteriorly	None
Case 2	F	N	3 (premature)	3	Respiratory distress, abdominal distention, cyanosis	No	Yes	Anterior wall	None*
Case 3	F	N	3	4	Abdominal distention	Yes	Yes	Greater curvature	None

*Two other muscle defects of the posterior gastric wall.

the onset of symptoms a laparotomy was performed. A large rent was found on the anterior gastric wall, extending from near the esophagogastric junction to the middle of the greater curvature. The edges of the tear were ragged and necrotic. The rent was repaired around a gastrostomy tube. The child did poorly and died 4 hours following operation.

An autopsy was performed 5 hours after death. The abdomen was slightly distended and the gastrostomy tube protruded through the operative incision. There was a small amount of exudate in the peritoneal cavity and the serosa of the abdominal viscera was covered with flecks of white curds. The wall of the stomach near the sutured defect was thinner than elsewhere. Except for inflammation of the serosa, the small and large intestines were not remarkable. The esophagus was normal. Generalized passive hyperemia and focal atelectasis were the other pathologic changes encountered. In the sections taken from the area of perforation there were autolysis and hemorrhage of the mucosa and the muscularis mucosa was intact. Intense edema and hyperemia, with focal areas of hemorrhage, were present in the submucosa. The muscular coat of the gastric wall ceased abruptly about 0.5 cm. from the site of perforation. Clumps of bacteria adhered to the external surface of the sutured area. Absence of the muscular coat was also noted in 2 sections taken from the posterior wall of the stomach, in areas where the gastric wall was not inflamed (Fig. 3). Where the muscularis was present it was normal microscopically and stained as muscle with the Mallory technique.

CASE 3.—A Negro girl, who weighed 2,490 grams at birth, was delivered spontaneously in the thirty-third week of gestation following premature rupture of the membranes. Gastric contents were aspirated at birth and feedings were started 12 hours following delivery. The child apparently was well until the third day, when abdominal distention was first noted. Gastric aspiration was performed and antibiotics were given. On the fourth day the child was cyanotic, the abdomen was markedly distended, and respirations were labored. Roentgenograms of the abdomen showed a large amount of free air in the peritoneal cavity. A laparotomy was performed. There was generalized peritonitis and a large rent in the stomach extended from high in the fundus to near the pylorus. The margins of the gastric wall about the rent were necrotic. The tear was closed. The child died 1 hour following operation.

The autopsy was performed 96 hours after death. There was only slight distention of the abdomen and a normal amount of fluid was found in the peritoneal cavity. Each pleural space contained about 25 ml. of blood-tinged fluid. The abdominal viscera were coated with fibrinous exudate. The lungs were passively congested and partially atelectatic. Sections of the stomach taken from the area of surgical repair revealed advanced mucosal autolysis with an intact muscularis mucosa. Sparse acute inflammation, but intense edema and congestion were present in the submucosa. The muscular coat was absent, and the transition from the area having a normal complement of muscle to that lacking it was abrupt. In a few of the sections, however, this transition was gradual and a few strands of smooth muscle were seen overlying the external surface of the defect.

DISCUSSION

Of the 17 reported cases, 11 occurred in males, 5 in females, and in 1 the sex was not stated. Other congenital anomalies were found in 4 patients and 7 infants were premature.

Additional defects were seen in the second case in areas far removed from the site of perforation and not associated with necrosis or inflammation of the gastric wall. Multiple defects were also described by Herbut[7] but have not been mentioned in the other reports of this entity. In our first case, the absence of muscularis was confined to the site of perforation. The transition from normal stomach to the region lacking muscle was usually abrupt,

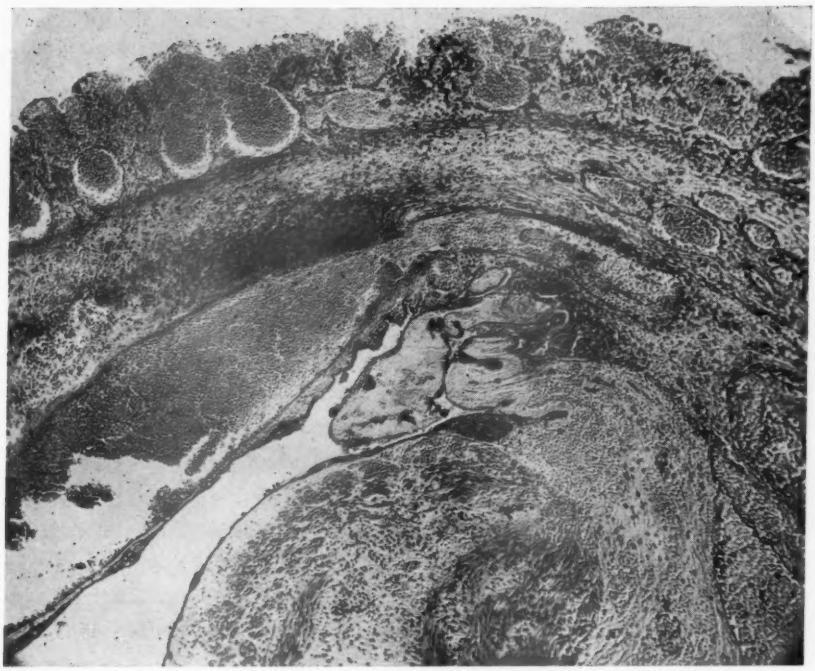


Fig. 2.—Section from the site of perforation in Case 1. A few attenuated muscle fibers bordering the defect are seen at the lower right. The entire wall is acutely inflamed. (Hematoxylin and eosin stain, ×50.)

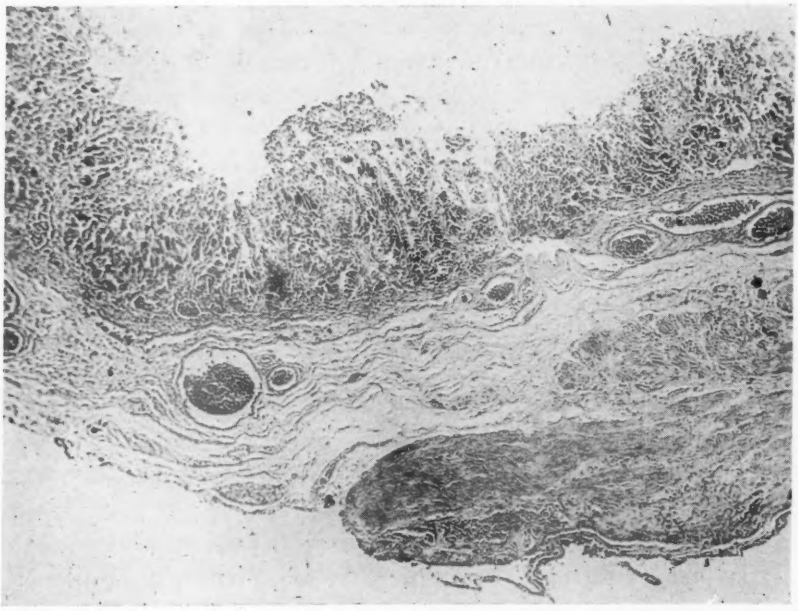


Fig. 3.—Area of absent muscle located in the posterior wall of the stomach in Case 2. (Hematoxylin and eosin stain, ×50.)

but in 1 case some of the sections revealed a few strands of smooth muscle overlying the anomalous region. The ends of the muscle bordering the defects were even and blunted, and sometimes tapered rapidly into bundles of much thinner diameter.

The anlage for the middle circular layer of gastric muscle is first seen in the 11 mm. embryo as an area of thickening of the mesenchyme at the ventral border (lesser curvature). In the 13 mm. stage similar thickenings appear in the fundus and in the dorsal border (greater curvature). The oblique fibers develop from the circular layer. The outer, longitudinal muscle is poorly developed at birth and may be completely absent. Some authors who doubt the existence of true congenital defects of gastric muscle claim that what is seen microscopically is mere separation of muscle fibers as a result of gastric dilatation. This interpretation does not explain satisfactorily the large size of some of these defects, their presence in stomachs with moderate or slight dilatation, and the absence of artefactual separation of muscle in the dilated stomachs of many other infants, with or without perforation of the wall.

Neonatal rupture of the stomach is an acute surgical emergency. The condition usually becomes manifest in the third to fifth day of life. Several days are required for gradual distention of the part lacking muscle. This eventually interferes with the blood supply and causes necrosis of the gastric wall and rupture. In most of these cases, respiratory difficulty has been the earliest and most prominent sign. This may be caused in part by gastric dilatation. Later, aspiration of gastric contents may be the most prominent sign.

Roentgenograms in the erect or lateral decubitus position, or both, will establish the diagnosis of ruptured hollow viscus. It is neither necessary nor desirable to instill barium or other contrast medium into the stomach. The diagnosis may be missed if only a recumbent film of the abdomen is obtained.

Though there have been several reported instances of survival after surgical closure in infants with neonatal gastric perforation, unfortunately in these cases no biopsy of the margin of the defect was obtained. However, all of the histologically confirmed cases of neonatal gastric perforation resulting from a congenital defect of musculature have had a fatal outcome. Such infants might be saved if the diagnosis of ruptured hollow viscus were established early and prompt surgical closure of the rent were performed. Too often the diagnosis is made when the infant is moribund, or at autopsy. The treatment is prompt surgical closure of the defect. A nasogastric tube is passed as soon as the diagnosis is made and gastric contents are aspirated. The stomach is kept decompressed, both to prevent further contamination of the peritoneal cavity and to reduce the likelihood of aspiration which so frequently occurs in infants who are vomiting. Vitamin K is administered. Supportive treatment with intravenously administered fluids, electrolytes, and blood, as well as antibiotics, oxygen, and an environment of high humidity are all important. In the acutely ill, premature infant, local infiltration of the abdominal wall with procaine is the safest anesthetic. Otherwise ether or cyclopropane, if

a skilled anesthesiologist is available, are the anesthetics of choice. An upper abdominal incision, transverse or longitudinal, is used. The latter is quicker to perform and close. Free fluid found in the peritoneal cavity is aspirated and specimens are obtained for culture and antibiotic sensitivity. The necrotic gastric wall about the margins of the perforation should be excised, and a 2-layer closure performed through healthy tissue. The peritoneal cavity is not drained unless an abscess is found. Postoperatively, continuous nasogastric suction is maintained until the return of peristalsis.

SUMMARY

A review of the literature discloses 14 cases of neonatal gastric rupture proved microscopically to have been caused by a congenital defect in the gastric musculature. To these we add 3 new cases. Clinical manifestations, with respiratory symptoms the most prominent, appear a few days after birth. A roentgenogram of the infant in the erect or lateral decubitus position establishes the diagnosis of ruptured hollow viscus with pneumoperitoneum. Awareness of this clinical and pathologic entity, with early diagnosis and prompt surgical closure, is the only means by which such infants might be saved.

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Reappraisal

CONDUCTED BY CLARENCE DENNIS, M.D. ASSISTED BY ALFRED HURWITZ, M.D.

THE ROLE OF INTESTINAL ANTISEPSIS IN THE PREOPERATIVE PREPARATION OF THE COLON

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IT IS the purpose of this article to assess whether or not intestinal antisepsis has any practical value. No attempt will be made to review the various substances which have been proposed as intestinal antiseptics. Recent editorials have questioned the need for the safeguards afforded by these antiseptic procedures. One of these was concerned mainly with the discussion of the use of antibacterial agents which have previously been shown to be unsatisfactory. The first requirement of an evaluation is that it must define the procedures under discussion and should, furthermore, be made in the light of the means by which the procedure is applied.

It is not possible to ascertain the operative mortality rate of colon surgery carried out by those operators who perform the major portion of the resections throughout the United States and the world at large. The true average mortality and morbidity rates are not those reported in papers from well-established major clinics and teaching institutions. A major clinic with a 3 per cent operative mortality rate will not realize the same numerical benefit from any improvement as will an individual physician whose mortality rate is 12 per cent. A similar situation exists concerning postoperative morbidity and convalescence.

Considerable resistance is being generated properly against the prophylactic use of antibacterial agents. The preoperative use of intestinal antiseptics is not to be considered prophylaxis any more than scrubbing the operative field with soap and water would be. There is no question of whether or not the gastroenteric tract is contaminated.

The proper use of intestinal antisepsis has greatly modified the course following operations on the colon. Characteristically the postoperative convalescence is essentially afebrile. There have been no instances of generalized peritonitis or fecal fistulas during the past 17 years in approximately 1,700 cases involving extensive operative procedures on the colon and only a single, recent instance of a local abscess at the line of suture.

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Practical methods for the practice of preoperative intestinal antisepsis have been available for 17 years.[14] Considerable experience has accumulated and specific procedures have been developed. A suitable intestinal antiseptic should have certain specific characteristics and properties. It is not imperative that all the desirable properties be possessed by a single substance, and these may be provided by a combination of agents. The latter must be selected carefully, because antibacterial agents may each cancel out the effectiveness of the other when given simultaneously, as in the case of the negation of neomycin by certain members of the tetracycline series.[8, 11] The combination neomycin-

TABLE I. GROUPING OF PATIENTS AND THE RESPECTIVE SCHEDULES FOR THE ADMINISTRATION OF NEOMYCIN-SULFATHALIDINE*

GROUP 1. NO OBSTRUCTION	GROUP 2. PARTIAL OBSTRUCTION	GROUP 3. COMPLETE OBSTRUCTION
Purgation not contraindicated	Purgation contraindicated	Preoperative bowel preparation contraindicated
Preparation in 20 hours	Gastric suction, decompression bowel movements re-established	Intra-abdominal trauma, bowel perforation, peritonitis
Castor oil 60 c.c., Neomycin 1.0 Gm. and Sulfathalidine 1.5 Gm. at 1:00 P.M.	When the obstruction has been relieved, give Neomycin 1.0 Gm. and Sulfathalidine 1.5 Gm. by mouth at 4 hour intervals until mechanical preparation of bowel has been accomplished. Usually requires a minimum of 3 days	Exploration as soon as general condition of patient warrants
Then Neomycin 1.0 Gm. and Sulfathalidine 1.5 Gm. at 2:00 P.M., 3:00 P.M., 4:00 P.M., 8:00 P.M., 12:00 P.M., 4:00 A.M., and 8:00 A.M.		Evacuate peritoneal cavity and add 200 ml. 0.5% Neomycin solution
Operation scheduled at 9:00 A.M.		Evacuate bowel and flood with as much as 1,000 ml. 1% Neomycin solution
		Place 100 ml. 0.5% Neomycin solution into peritoneal cavity at time of closure
		Wash wound with 0.5% Neomycin solution during closure
No additional time required for intestinal antisepsis: when mechanical preparation completed bowel essentially sterile†		
Intestinal antisepsis maintained throughout period of postoperative paralytic ileus without the administration of additional drug		
If the bowel has been sutured, Neomycin 1.0 Gm. and Sulfathalidine 1.5 Gm. are started again as soon as peristalsis has returned. Medication on a 4 hour schedule 9 to 12 days postoperatively		
Intestinal antisepsis is terminated by discontinuing the Neomycin 2 days prior to stopping the administration of Sulfathalidine		

*Modified from Poth.[14]

†The preparation presented is the total local preoperative preparation required.

Sulfathalidine is the most effective and has given no major adverse complications. There has been not a single instance of staphylococcal invasion of the bowel with development of pseudomembranous enteritis during the 10 years this combination has been used in this institution. The combination should, without any change whatsoever, be administered according to a previously

published schedule, Table I. Neither neomycin nor Sulfathalidine is readily absorbed from the bowel and remains to suppress bacterial growth throughout the postoperative period of paralytic ileus, during which time oral ingestion is proscribed. It cannot be stressed too emphatically, should complications be encountered, that the substances used and the schedule of their administration must be determined.

The antibacterial agents are of importance. The frequency of administration also must be strictly observed to maintain suppression of bacterial growth in an environment as favorable as that afforded by the bowel. Unsustained suppression of bacterial growth permits the outgrowth of the more resistant microorganisms. During preoperative preparation the doses should not be spaced more than 4 hours apart, otherwise the effective agent will be swept out of the small intestine, leaving an environment favorable to uninhibited bacterial growth. Again, suppression will not be sustained if a combination of antibacterial agents is used and one or more of the agents is absorbed from the bowel, making those which remain ineffective during the all-important period of early healing while postoperative paralytic ileus persists.[3, 4] Neomycin and Terramycin form such a combination. Furthermore, there are indications that Terramycin actively stimulates the growth of *Staphylococcus aureus* in the bowel.[8]

Suitable intestinal antiseptics are not absorbed from the intestine. Nonabsorption permits ingestion in whatever quantities are needed without toxicity to the host.

Intestinal antiseptics may be bacteriostatic or bactericidal agents. Sulfathalidine is a bacteriostatic agent while neomycin is readily maintained in the bowel under therapeutic conditions in concentrations which are bactericidal.

Effective reduction of the intestinal bacterial flora will result regularly in the proliferation of yeasts which may, on occasion, cause local irritation and diarrhea controllable by oral and local administration of Vioform. Infrequently nystatin will be required to control a monilial infestation. Occasionally, perianal excoriation will require local application of hydrocortisone-Vioform ointment. Yeast infestations are a nuisance rather than a dangerous complication.

SPECIFIC BENEFICIAL EFFECTS OF INTESTINAL ANTISEPSIS

One of the most basic observations illustrating the value of intestinal antisepsis is its influence on the healing of the suture line in the bowel.[16] Intestinal antisepsis changes the usual secondary repair of the anastomotic wound of the bowel to primary healing. Furthermore, the alteration and attenuation of the intestinal flora readily attained and sustained will protect an ischemic bowel against necrosis by preventing thrombosis of the small blood vessels.[18] The magnitude of destruction of the bowel when the flora are unaltered is such that the degree of protection afforded by the antibacterial agents is amazing.

Another instance of the effect of intestinal antiseptics is illustrated by the following experiment: The mesentery of a 10 cm. segment of distal ileum of the dog, together with its arteries and veins, is divided so that the only remaining vascular supply is conveyed via the intestinal wall. The segment of ileum

is transected centrally and anastomosed (Fig. 1). The results were: 100 per cent death of control animals due to disruption of the suture line and 100 per cent survival of animals protected by neomycin-Sulfathalidine intestinal antisepsis (Fig. 2).

Table II summarizes the results of resection and primary open anastomosis of 192 consecutive cases of carcinoma of the colon. Attention is directed toward the very low wound infection rate and the benign postoperative temperature elevation. This effect is even more striking when, in addition to the oral administration of the antibacterial agents, the peritoneal cavity and abdominal wound were irrigated with aqueous solutions of neomycin. Comparison between these open bowel resections and anastomoses and routine cholecystectomy without neomycin irrigations showed less elevation of temperature postoperatively in the bowel operations. These observations could be explained only by the assumption that the neomycin irrigations conferred some general systemic protection because of absorption from peritoneal cavity and wound.

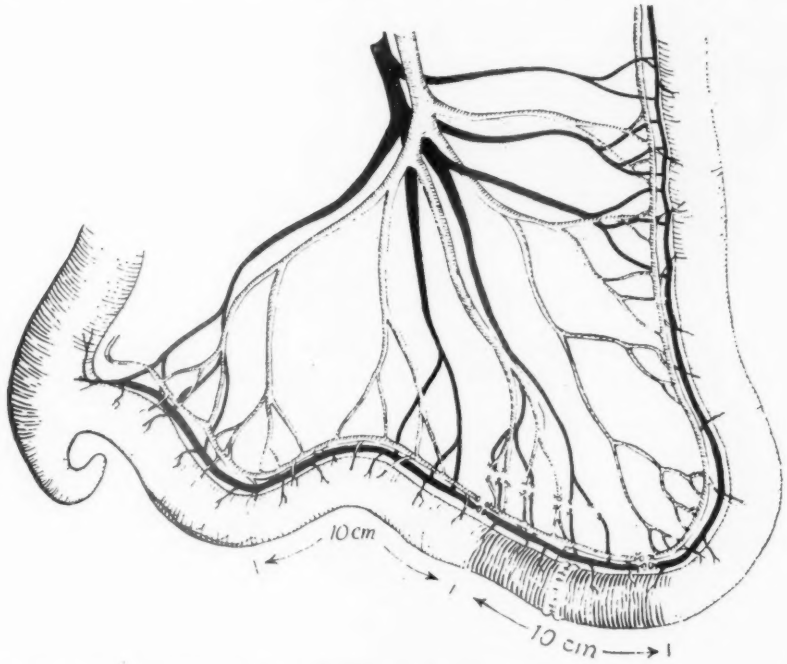


Fig. 1.—An experimental test object to study the influence of antibacterial agents on healing of ischemic bowel. The arteries and veins in the mesentery of a 10 cm. segment of ileum are divided and ligated. The segment is 10 cm. proximal to the termination of the artery arising at the ileocecal valve and running proximally along the antimesenteric border of the ileum as illustrated. The only vascular supply is in the wall of the ileum. The ischemic segment becomes prominently and abruptly cyanotic. This segment is sectioned in its midlength and reanastomosed with a single row of interrupted, inverting, nonabsorbable sutures. The results are given in Fig. 1.

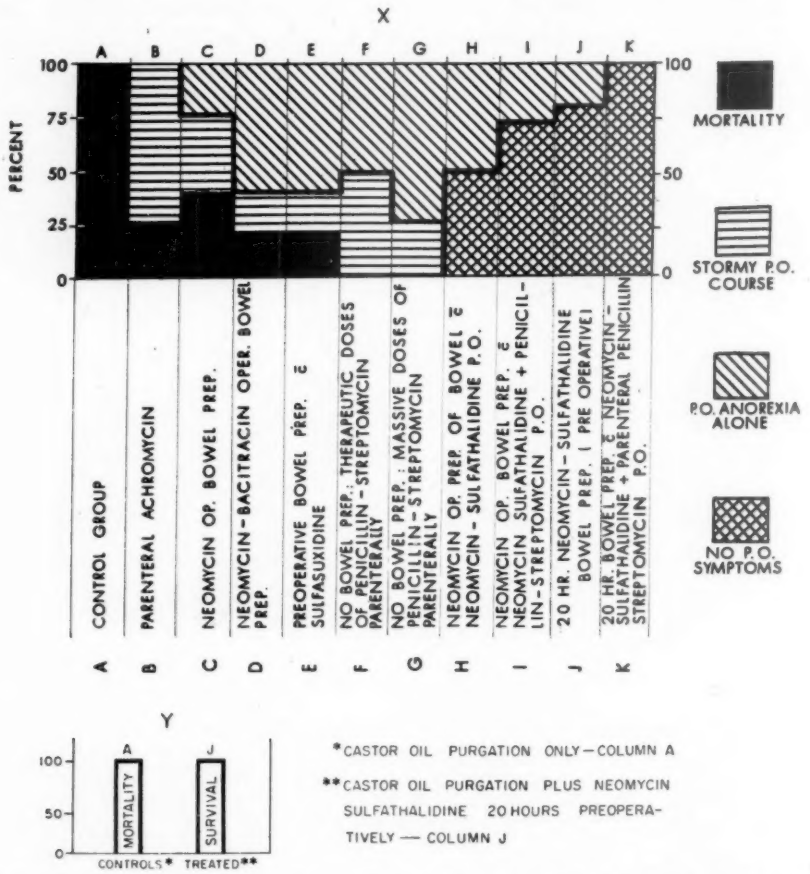
Subsequently, Singleton, Davis, and Julian[19] studied the effectiveness of various irrigating solutions in reducing infection of contaminated deep experimental wounds in guinea pigs. They found neomycin solutions to be the most effective (Table III). In fact, they observed that the irrigation of one wound would significantly reduce the rate of infection of another remote, untreated, contaminated wound following the infliction of several wounds simultaneously in the same animal. Poth, Miller, and Dunlap showed the protection rendered

against the development of infection of contaminated experimental deep wounds in guinea pigs by the intraperitoneal administration of a single tolerated dose of 0.5 per cent neomycin solution (Table IV).

It is maintained that these observations are significant and indicate the beneficial influence of proper and adequate intestinal antisepsis, as well as the adjuvant irrigation of the soiled peritoneum and soft tissue wounds with neomycin solutions.

UNUSUAL INDICATIONS FOR THE USE OF INTESTINAL ANTISEPTICS

There are indications for the use of intestinal antiseptics when systems other than the gastrointestinal tract are involved. A deeply jaundiced patient undergoing an intra-abdominal operation will benefit greatly from preoperative intestinal antisepsis. Two vascular procedures also demand adequate preoperative intestinal antisepsis. Correction of coarctation of the thoracic aorta may be


X
A B C D E F G H I J K
100
75
50
25
0
PERCENT
100
50
0
MORTALITY
STORMY P.O. COURSE
P.O. ANOREXIA ALONE
NO P.O. SYMPTOMS
A CONTROL GROUP
B PARENTERAL ACHROMYCIN
C NEOMYCIN OP. BOWEL PREP.
D NEOMYCIN - BACITRACIN OPER. BOWEL PREP.
E PREOPERATIVE BOWEL PREP. & SULFASUXIDINE
F NO BOWEL PREP.; THERAPEUTIC DOSES OF PENICILLIN - STREPTOMYCIN PARENTERALLY
G NO BOWEL PREP.; MASSIVE DOSES OF PENICILLIN - STREPTOMYCIN PARENTERALLY
H NEOMYCIN OP. PREP. OF BOWEL & NEOMYCIN - SULFATHALIDINE P.O.
I NEOMYCIN OP. BOWEL PREP. & NEOMYCIN SULFATHALIDINE + PENICILLIN - STREPTOMYCIN P.O.
J 20 HR. NEOMYCIN - SULFATHALIDINE BOWEL PREP. (PRE OPERATIVE)
K 20 HR. BOWEL PREP. & NEOMYCIN - SULFATHALIDINE + PARENTERAL PENICILLIN STREPTOMYCIN P.O.
Y
100
50
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MORTALITY
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TREATED**
*CASTOR OIL PURGATION ONLY — COLUMN A
**CASTOR OIL PURGATION PLUS NEOMYCIN SULFATHALIDINE 20 HOURS PREOPERATIVELY — COLUMN J

Fig. 2.—The results of various antibiotic agents as they influence the healing of ischemic ileum in the experimental procedure depicted in Fig. 1.

followed by diffuse necrotizing periateritis nodosa of the portal system and can cause extensive fatal intestinal necrosis. The course of this complication will be significantly modified when the bacteria have been eliminated from the bowel. Smith and Szilagyi[20] recently reported necrosis of the sigmoid following excision of aneurisms of the lower abdominal aorta. The ischemic necrosis is

TABLE II. 192 CONSECUTIVE CASES OF CARCINOMA OF COLON TREATED BY PRIMARY OPEN ANASTOMOSIS

GROUP*	NO. OF CASES	BOWEL PREPARATION	OPERATIVE MORTALITY	P.O. TEMP.† 101° F. (%)	WOUND INFECTIONS (%)
1 and 2	18	Mechanical preparation using castor oil and enemas. All cases received parenteral antibiotics postoperatively	11%	100	77.7
1 and 2	35	No purgation or enemas. Sulfasuxidine 3.0 Gm. q 4 hours for 7 days. Parenteral antibiotics only if temperature exceeds 101° F. rectally	0	54	5.7
1 and 2	58	Neomycin-Sulfathalidine orally, preoperatively—divided about 25% (group 2) and 75% (group 1). Parenteral antibiotics only if temperature exceeds 101° F. rectally	0	35	3.4
1 and 2	59	Neomycin-Sulfathalidine orally preoperatively. Peritoneal cavity and abdominal wound irrigated with 0.5% Neomycin solution. Parenteral antibiotics only if temperature exceeds 101° F. rectally	0	26	1.7
3	22	Group 3—no preoperative preparation of the bowel possible. Bowel partially decompressed at time of operation. Bowel filled with 1% Neomycin solution at time of operation. Peritoneal cavity and abdominal wound irrigated with 0.5% Neomycin solution. Resection and primary anastomosis performed in the presence of complete obstruction and distention of proximal bowel. No decompressing enterostomies. Parenteral antibiotics usually given both pre- and postoperatively	0	36	9.1

*This grouping refers to the schedule presented in Table I. Groups 1 and 2 are charted together since there is no essential difference in the results of the 2 groups.
†Rectal temperature readings of 101° F. or more on one or more occasions postoperatively.

TABLE III. PROTECTION OF GUINEA PIGS FROM WOUND INFECTIONS FOLLOWING FECAL CONTAMINATION BY IRRIGATIONS[19]

NO. OF INCISIONS	TREATMENT	% INFECTED
76	Controls	82.8
24	3% iodine, 100 c.c.	41.7
41	Clorpactin, 100 c.c.	41.5
45	Saline, 100 c.c.	51.1
40	2% Sulfamylon, 100 c.c.	40.0
38	20% Sulfamylon, 100 c.c.	23.7
33	1% neomycin, 100 c.c.	3.0

TABLE IV. PROTECTION OF GUINEA PIGS AGAINST WOUND INFECTION DUE TO FECAL CONTAMINATION* AFFORDED BY INTRAPERITONEAL INJECTION OF 0.5% NEOMYCIN SOLUTION

NO.	TREATMENT	% INFECTED†
18	Controls	72.5
11	0.25 Gm./kg.	9
10	0.0625 Gm./kg.	20
10	0.03125 Gm./kg.	40

*One cubic centimeter of 10% fecal filtrate instilled into a closed, deep wound on the back.
†Actual pus formation and tissue necrosis.

progressive and appears several days postoperatively. It can be expected that intestinal antisepsis will offer protection against this complication. It is strongly urged that neomycin-Sulfathalidine be given both before and after operation whenever the blood supply to the bowel may possibly be embarrassed. These antibacterial agents should be administered in full therapeutic doses whenever mesenteric thrombosis is suspected. The use of the parasympatholytic drugs, such as Pamine, to control the diarrhea caused by neomycin-Sulfathalidine will protect the operative field following excision of pilonidal cysts and perianal skin grafting.

Most early fecal fistulas will heal spontaneously when the intestinal flora is suppressed by adequate intestinal antisepsis.

THE NUISANCES, INCONVENIENCES, AND HAZARDS OF INTESTINAL ANTISEPSIS

Intestinal antisepsis imposes certain untoward manifestations. Do they overshadow the beneficial influences?

First, conditions for attaining adequate intestinal antisepsis are relatively concise. It is necessary to appreciate these restrictions and operate within their limits if the best results are to be obtained. It is disconcerting to find any useful procedure being condemned by individuals who either are not cognizant of what is actually recommended and required or who find it inconvenient to proceed in the prescribed manner which has been shown to give good results. If the conditions and limits of any procedure are changed, it is imperative that whoever advocates the changes must fully understand the original procedure, must have tested its limitations, and must assume fully the responsibility for any and all modifications proposed. Personal annoyance with a useful procedure does not justify destructive, unsupported disapproval.

Drastic reduction of bacteria in the bowel is always followed by the outgrowth of yeasts if fungicides are not administered. Yeast infestations may cause diarrhea and local perianal irritation, which constitute nuisances rather than serious hazards. A more hazardous situation arises when the antibacterial agent used as an intestinal antiseptic allows pathogenic strains of organisms to proliferate, as illustrated by the outgrowth of staphylococci, which elaborate enterotoxins and precipitate pseudomembranous enterocolitis. This complication has not, to my knowledge, occurred when the combination neomycin-Sulfathalidine has been used as outlined in this and other publications by the author.

The hazard of implantation and survival of malignant cells at the site of anastomosis recently emphasized by Cole[5, 6, 7, 23] and others[1, 21, 22] may well be augmented by intestinal antiseptics. Both the frequency of implantation and the likelihood of transplantation would logically be increased in a medium essentially devoid of bacteria. Boerema[2] made this supposition in 1950. The experiments of Vink[24] in 1953 on rabbits would indicate that this suggestion may well be correct. In our laboratories Jacobsen[17] studied the effectiveness of several solutions with regard to their capacity to destroy free-floating and attached cells in tissue culture, as well as the irritation caused by these solutions when used to bathe segments of bowel during anastomosis. Healing at the line of suture was observed also. Dakin's solution diluted 50 times kills free-floating and

attached cancer cells on contact. Dakin's solution causes no irritation to the mucous membrane of the colon nor does it retard healing of the anastomosis after prolonged contact. Half-strength Dakin's solution is being used clinically as an irrigant in the lumen of the bowel without untoward effects. The lesion is isolated between ties of ¼ inch bias tape within the length to be resected at the earliest moment. Proximally and distally 15 cm. from the tapes the lumen is occluded with Dixon clamps following which the bowel is filled with half-strength Dakin's solution. The lines of resection are placed in these sections of bowel. Unattached cells are killed by half-strength Dakin's solution. This solution will expose cells adherent to the mucosa and covered by mucus. A significant advantage of using half-strength Dakin's solution for its cancerocidal effect is the ready availability of the solution in any operating theater, not to mention its pronounced antiseptic properties. Particular attention should be directed toward the possibility of deep implantation of tumor cells by through-and-through sutures. Deeply implanted cells are much more likely to become transplanted. Our observations to date are insufficient for the drawing of conclusions, but past observations would indicate that tumor implantation and transplantation occur sufficiently frequently both with and without intestinal antisepsis to demand precautions against them. The experimental evidence indicates that Dakin's solution is safe and affords complete protection when properly used.

RESPIRATORY SUPPRESSION BY NEOMYCIN

This subject is not properly a part of this paper on intestinal antisepsis, but it should be included because intraperitoneal and wound irrigations are closely associated with surgery of the colon. The potential hazard of large doses of neomycin was suggested in March, 1951.[15]

" . . . it is necessary to issue a warning against placing large quantities of neomycin in the peritoneal cavity of man, because, while 3,000 gamma will protect a 20 gram mouse from the tremendous insult of the introduction of a fatal quantity of feces into the peritoneal cavity, 5,000 gamma of the antibiotic will, of itself, kill the mouse."

The following discussion was written especially for this presentation by Dr. Leo S. M. Duplot of the Department of Anesthesiology:

"Pittinger and Long[12] determined that a dosage of 2 mg. per kilogram body weight in rabbits could produce total neuromuscular blockade when a 50 per cent block was already present with ether. These authors also showed that neomycin, ether, and curare were mutually potentiating. Combinations of these drugs are likely to reach peak blood levels at the end of an operation when anesthesia is deepened or curare is added to facilitate peritoneal closure. Additional neomycin is used at this time to wash out a contaminated wound. When neomycin has been introduced previously into the contaminated peritoneal cavity, systemic absorption of neomycin in a patient under ether anesthesia can lead to respiratory depression which may be prolonged and profound. This case illustrates the effect of ether and neomycin on respiratory adequacy:

A 4½ pound (2 kilogram) 1-day-old infant underwent a surgical procedure for repair of congenital atresia of a portion of the small intestine.[14] No premedicant drugs were given. Anesthesia was maintained with endotracheal ether in an open, nonrebreathing system. Spontaneous respiration was adequate during the period of the operation and peritoneal closure.

One per cent neomycin solution was used intraperitoneally during the operation. After peritoneal closure, the abdominal wound was irrigated with 50 mg. of neomycin in 0.5 per cent solution. Practically all of this solution spilled out of the wound. Although no other muscle relaxants had been given during the procedure, muscle tone disappeared and respiration became very shallow. Positive pressure breathing was required for 30 minutes. The endotracheal tube was removed after 6 hours and the child recovered without further complications.

"The mechanism of action resembles curare in that a "competitive" type of neuromuscular block is induced. Curare and neomycin presumably combine with receptors at the motor end-plate which ordinarily act to block the action of acetylcholine.

"The neuromuscular blocking agents such as decamethonium and succinylcholine exhibit a "dual" action at the motor end-plate. These drugs prevent normal breakdown of acetylcholine resulting in a persistent depolarization at the end-plate region. This action is termed "Phase I." "Phase II" occurs following prolonged administration of depolarizing agents at which time a curare-like block is manifested. Under a "Phase II" block, neomycin would potentiate decamethonium and succinylcholine and vice versa. Eckenhoff[9] has reported a case of respiratory depression following succinylcholine and neomycin.

"Pittinger and Long[13] studied the action following intravenous administration of 11 antibiotics, evaluating both their neuromuscular blocking and hypotensive actions quantitatively in rabbits. Both actions are possessed by streptomycin, dihydrostreptomycin, neomycin, kanamycin, and polymyxin B. The neuromuscular blocking action of streptomycin, dihydrostreptomycin, and neomycin is effectively neutralized by neostigmine methylsulfate which, however, enhances this action in the cases of kanamycin and polymyxin B. It is imperative that this difference in action of neostigmine methylsulfate be correctly assessed when respiratory depression induced by one or the other of these 2 groups of antibiotics is treated. While bacitracin, erythromycin, oleandomycin, and tetracycline are not neuromuscular blocking agents, they do have hypotensive activity.

"Postoperative respiratory depression occurs rarely as a direct result of neomycin absorption. Neomycin has been innocuously used in thousands of cases under all types of anesthesia. Before concluding that neomycin has caused respiratory embarrassment the following more common factors which cause inadequate respiration should always be evaluated and interpreted: (1) preanesthetic medication with opiates, barbiturates, or ataractics, (2) muscle relaxants such as curare, decamethonium, succinylchloride, (3) the physiologic and metabolic effects of anesthetic drugs and techniques including spinal, regional, and local, (4) prolonged effects of carbon dioxide accumulation and hypoxia occurring as a result of hypoventilation during the anesthetic period, (5) alteration of the response of the respiratory center to normal stimuli following prolonged passive or controlled respiration, and (6) mechanical interference with breathing by tight dressings or malposition of the patient.

"If the weight of evidence shows that neomycin is the cause of hypoventilation an antagonist may be administered. Neostigmine and edrophonium are effective antagonists and probably act by prolonging the life of acetylcholine.

Edrophonium therapy should be tried before neostigmine for 2 reasons. First, edrophonium has a short duration of action. If no response occurs, respiratory depression is probably not due to neomycin. Second, there are no muscarine-like actions of this drug, and therefore it need not be preceded by atropine. If the response to edrophonium is favorable then neostigmine preceded by atropine will give a more prolonged action. Overtreatment with neostigmine and atropine should be avoided. Gray[10] has reported cases of cardiac arrest following the use of these 2 drugs. Regardless of the response to antagonist therapy, adequate ventilation must be maintained by intermittent positive pressure as long as necessary until the causative agent has been determined and the effects have worn off."

Respiratory depression can be prevented by avoiding deep ether anesthesia or curarization at a time when neomycin may be systemically absorbed, and by reducing the dosage of neomycin according to the patient's weight. A few milligrams absorbed by a premature infant under ether anesthesia may produce significant additional depression.

In actual practice large quantities of 0.5 per cent neomycin sulfate solutions have been used to irrigate the peritoneal cavity throughout operation in several thousands of cases without respiratory paralysis except in the 1 instance of the 1-day-old infant cited above. There have been no deaths at this institution from respiratory failure. Little or none of the solution is left in the peritoneal cavity on closure. If an active peritonitis exists, a 0.25 per cent solution is used. This more dilute solution is, in all probability, just as effective as is the 0.5 per cent solution.

SUMMARY

It seems superfluous to discuss the question of whether or not intestinal antisepsis has any practical value. I believe the results of the application of the procedure presented are ample proof of its usefulness at both the experimental and clinical levels.

A reference to the most satisfactory antibacterial agents available is in order. The sulfonamides are too slow acting and are only bacteriostatic agents. Streptomycin, neomycin, and kanamycin are the only broad-spectrum antibiotics with bactericidal properties which are not absorbed from the gastrointestinal tract and are therefore suitable for consideration. The intestinal flora rapidly acquires resistance to streptomycin and it is eliminated from further consideration. Kanamycin has been available for only a short time, but unfortunately, bacterial resistance to it is already appearing. What is even more serious, its use is establishing cross-resistance in bacteria against other antibiotics, including neomycin. Therefore, kanamycin should not be advocated for general use as an intestinal antisepsic.

A warning is issued against spacing the dosage of an intestinal antiseptic beyond a 4 hour frequency, because the drugs will not be maintained in the upper small bowel in sufficient concentration to suppress bacterial growth, and conditions favorable for the outgrowth of the relatively more resistant organisms will be established.

The cancerocidal action of Dakin's solution is cited, and its use in the bowel at the time of operation as a safeguard against transplantation of tumor cells at the line of anastomosis is presented.

An appeal is made for the safe and proper use of dilute neomycin solutions for irrigating the contaminated and infected abdominal cavity and extensive soft tissue wounds. The results of long and extensive experience are given together with evidence for the efficacy of the practice. The nature of possible complications and the manner of their management are described.

It is contended that the proper use of neomycin and Sulfathalidine as a combination is adequately worth while and confers a high degree of protection against infection in any procedure which may embarrass the blood supply of bowel.

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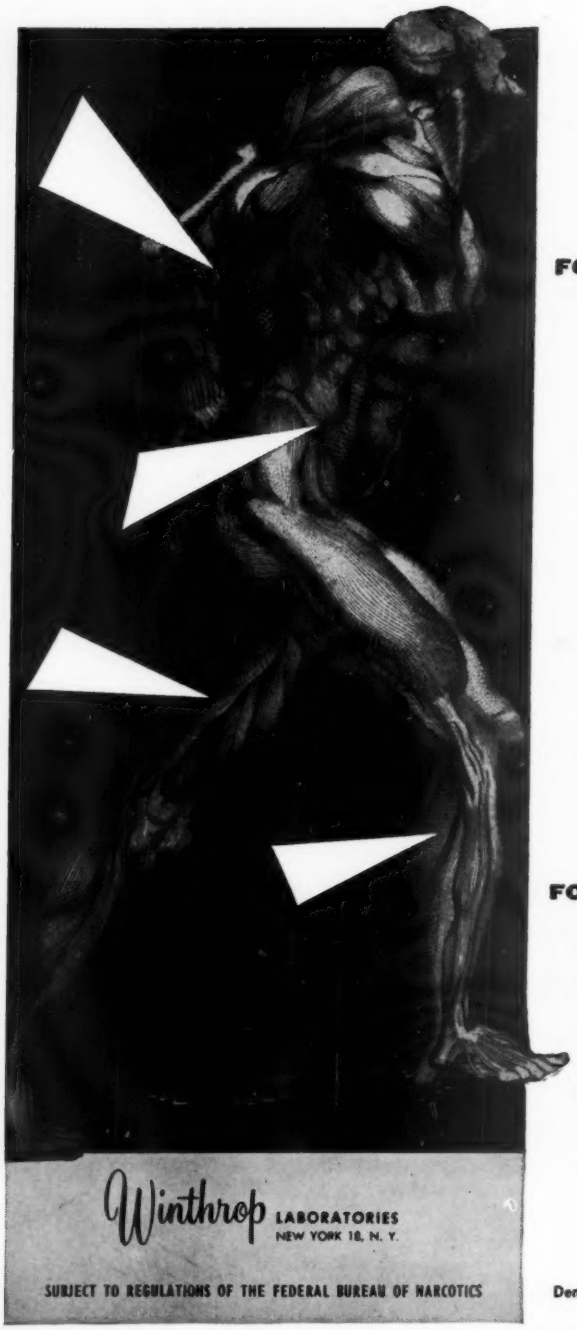

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References: 1. Sollmann, T.: A Manual of Pharmacology, 8th Ed., W. B. Saunders Company, Philadelphia, 1957, p. 1004. 2. Hill, F.: Practical Fluid Therapy in Pediatrics, W. B. Saunders Company, Philadelphia, 1954, p. 104. 3. Harper, J. Y. and Pomerat, C. M.: In Vitro Observations on Behavior of Conjunctival and Corneal Cells in Relation to Electrolytes, American Journal of Ophthalmology 46:269-275, 1958. 4. Pomerat, C. M., and Overman, R. R.: Electrolytes and Plasma Expanders, I. Reaction of Human Cells in Perfusion Chambers With Phase Contrast Time-Lapse Cine Records, Zeitschrift fur Zellforschung, Bd. 463 2-17, 1956. 5. Hild, W.: Ependymal Cells in Tissue Culture, Zeitschrift fur Zellforschung, Bd. 468 259-271, 1957. 6. Rice, C. O.: Personal Communication. 7. DeWeese, M. S., and Hodgson, P. E.: Personal Communication. 8. Shambaugh, G. E. Jr.: Technical Problems in Surgical Treatment of Otosclerosis, J. Internat. Coll. Surgeons 25:772-776 (June) 1956.

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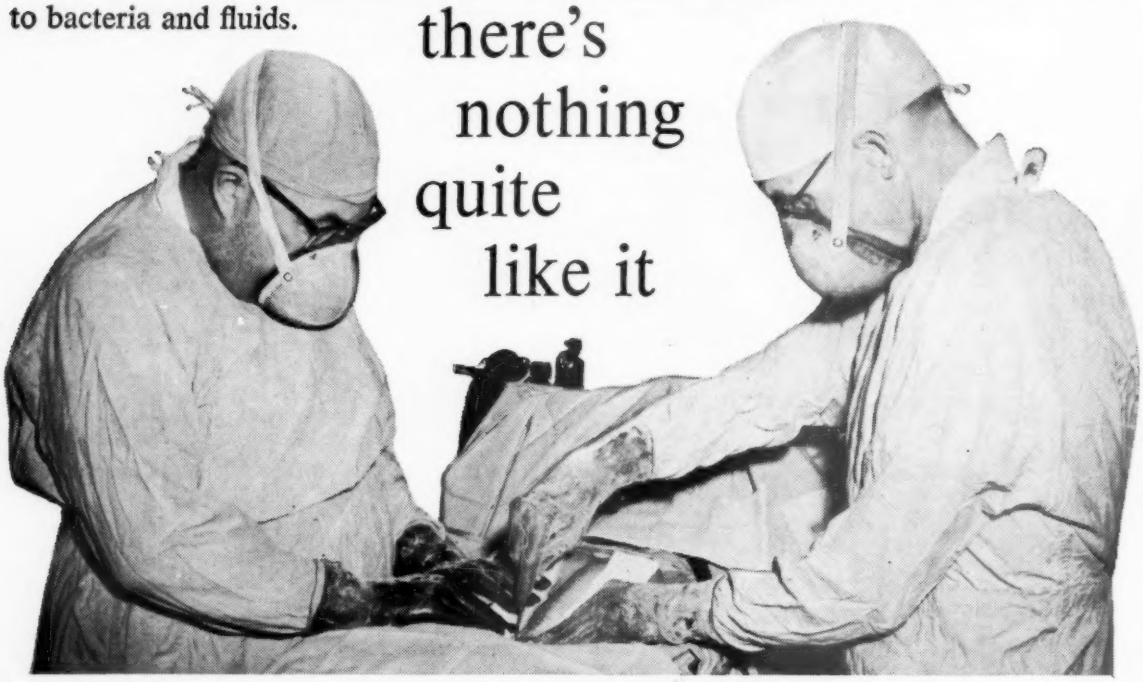

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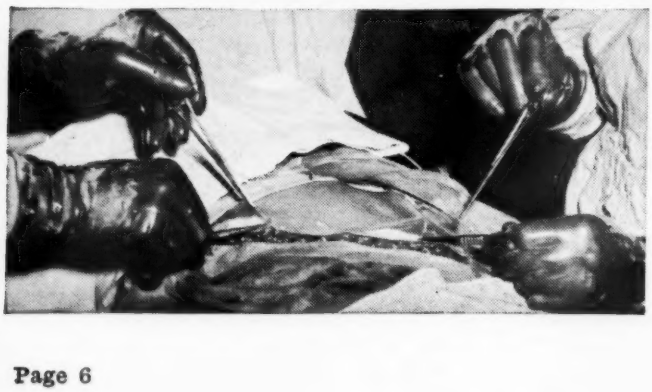


At closure suturing is completed to skin level, then the transparent film is peeled back from wound edges, and skin suturing completed before the entire film is peeled off. Some surgeons prefer to suture right through the film, leaving a small piece intact under the sutures. Following either method, Aeroplast® Surgical Dressing can be sprayed on as the definitive dressing. It forms a tough but flexible plastic film dressing impermeable to environmental contamination and requiring infrequent changes.

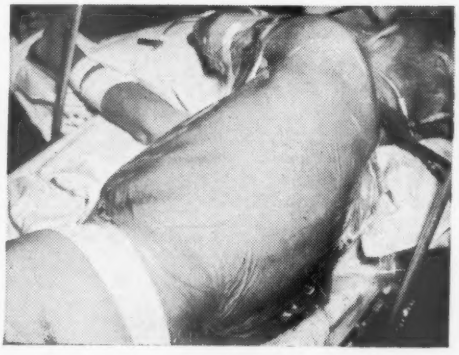
Photos at left and above courtesy Ralph Adams, M. D., Boston, Mass. and Wolfeboro, N. H.

Basic technic When freshly "prepped" skin is dry, Vi-Hesive Adherant is sprayed on to an even pink tint from about 12" distance. Sterilized Vi-Drape Film is held taut over proposed operative area then smoothly molded by hand to site and wide adjacent skin area. Photo courtesy Ralph Adams, M.D.

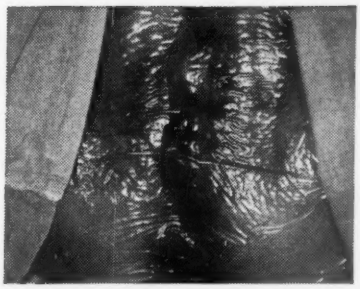
Sealing off the contaminated colostomy or ileostomy, and yet having it visible while exploring a new operative field, is made possible by the application of Vi-Drape Film to the entire area. Photo courtesy of Robert M. Zollinger, M. D., William G. Pace, M. D. and Marjorie J. Reed, R. N., Columbus, Ohio.

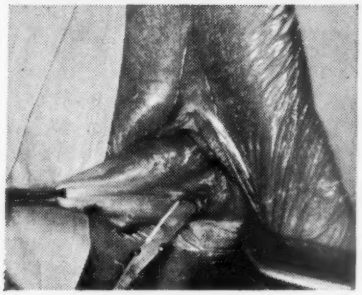
Visibility of landmarks, maintenance of asepsis in operative areas previously hard-to-drape, and isolation of the entire operative zone are particular surgical advantages of using Vi-Drape Film in neurosurgery. Illustrative is the isolation of the cervical occipital area for laminectomy shown above. Photo courtesy Arthur B. Eisenbrey, M. D., Detroit, Mich.

Smooth molding and close adherence of the plastic film to the difficult contour of the hip, provides an aseptic operative area previously considered almost impossible to achieve. Vi-Drape Film clings closely to the skin throughout long procedures. Photo courtesy Chas. G. Lovingood, M. D., Frank L. Shively, Jr., M. D. and Albert M. Storrs, M. D., Dayton, Ohio.



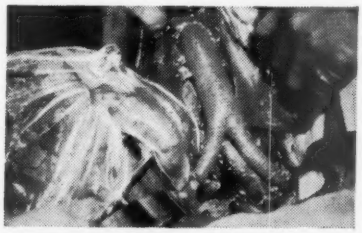
Large areas can be sealed off for thoracic or cardiovascular surgery without hiding landmarks. Neck and shoulders are completely isolated from the incision. A cleaner, drier operative field is possible using Vi-Drape Film. When Aeroplast Surgical Dressing is used postoperatively, evaluation of healing can be made without removing dressings. Photo courtesy Curtis P. Artz, M.D., Jackson, Miss.





Isolation of the anal area from the vaginal orifice during correction of prolapse of the vaginal vault avoids contamination by fecal extrusions.

Exteriorized vaginal vault is protected from contamination by Vi-Drape Film clinging closely to vaginal orifice during procedure and by isolation of the anus. Photos courtesy C. Paul Hodgkinson, M. D., Detroit, Mich.



To prevent trauma, desiccation and infection — Vi-Drape Film is frequently used as a protective wrap for exposed organs as shown above holding intestines during an aortic graft. Photo courtesy Chas. G. Lovingood, M. D., Frank L. Shively, Jr., M. D. and Albert M. Storrs, M. D., Dayton, Ohio

Would you like to see a full-color sound motion picture further illustrating the application of Vi-Drape Film in varied surgical procedures? The film, "A New Transparent Plastic Surgical Drape," produced by Robert M. Zollinger, M.D., William G. Pace, M.D. and Marjorie J. Reed, R.N., at Ohio State University Department of Surgery, is available for showing to all members of the surgical team.

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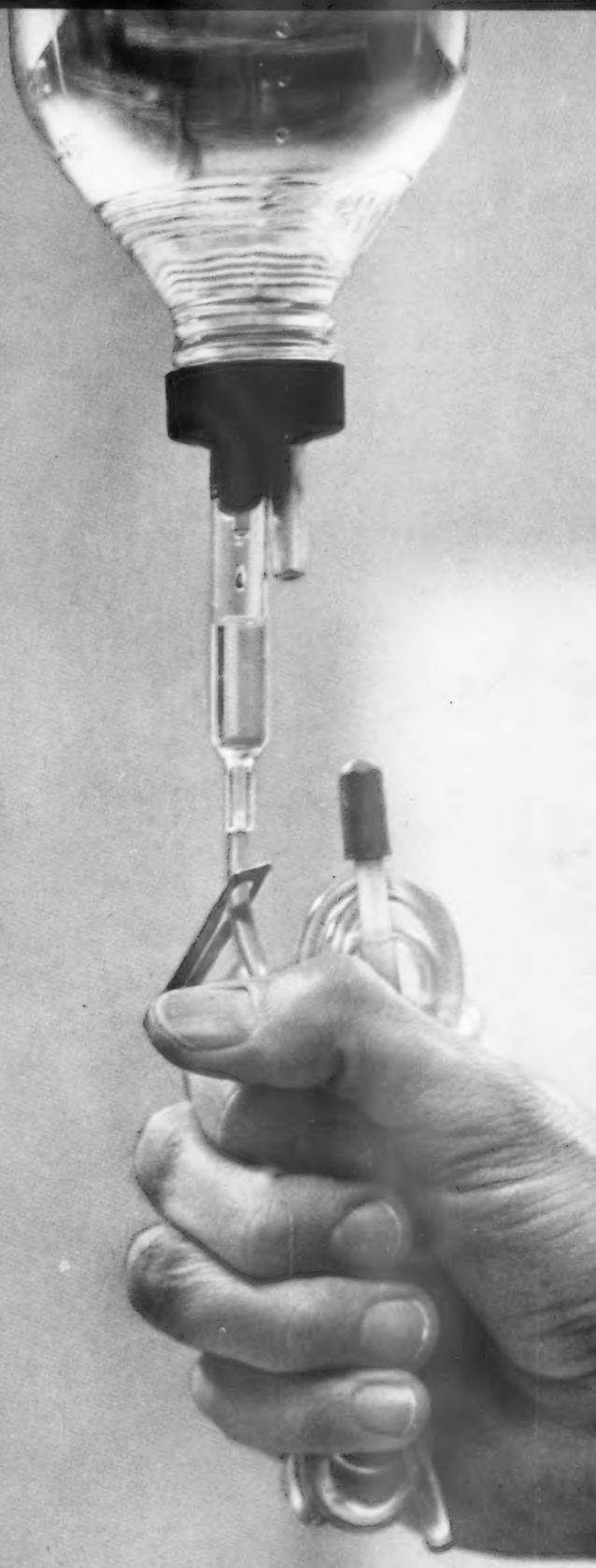

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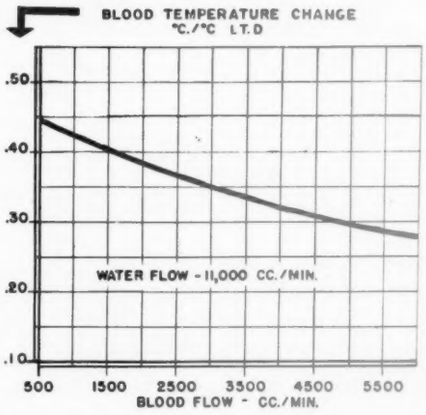

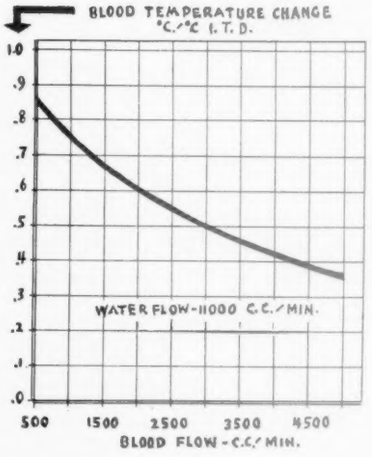

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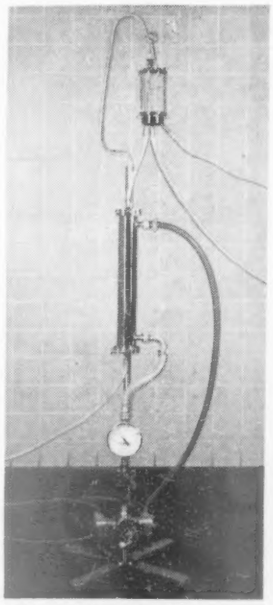

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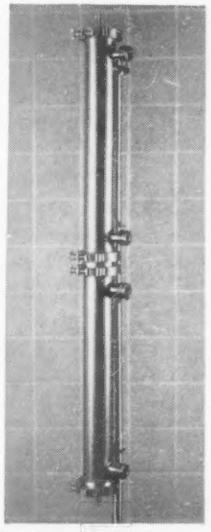

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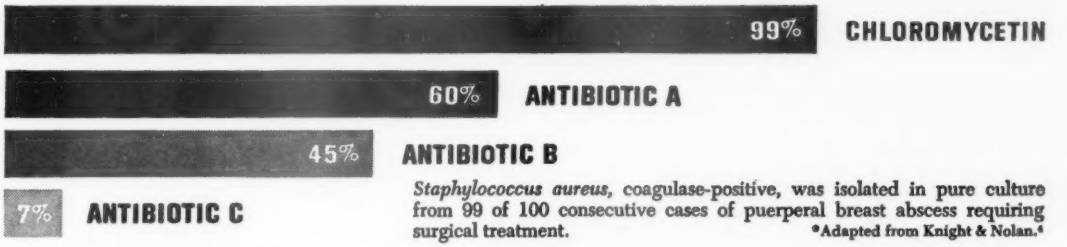

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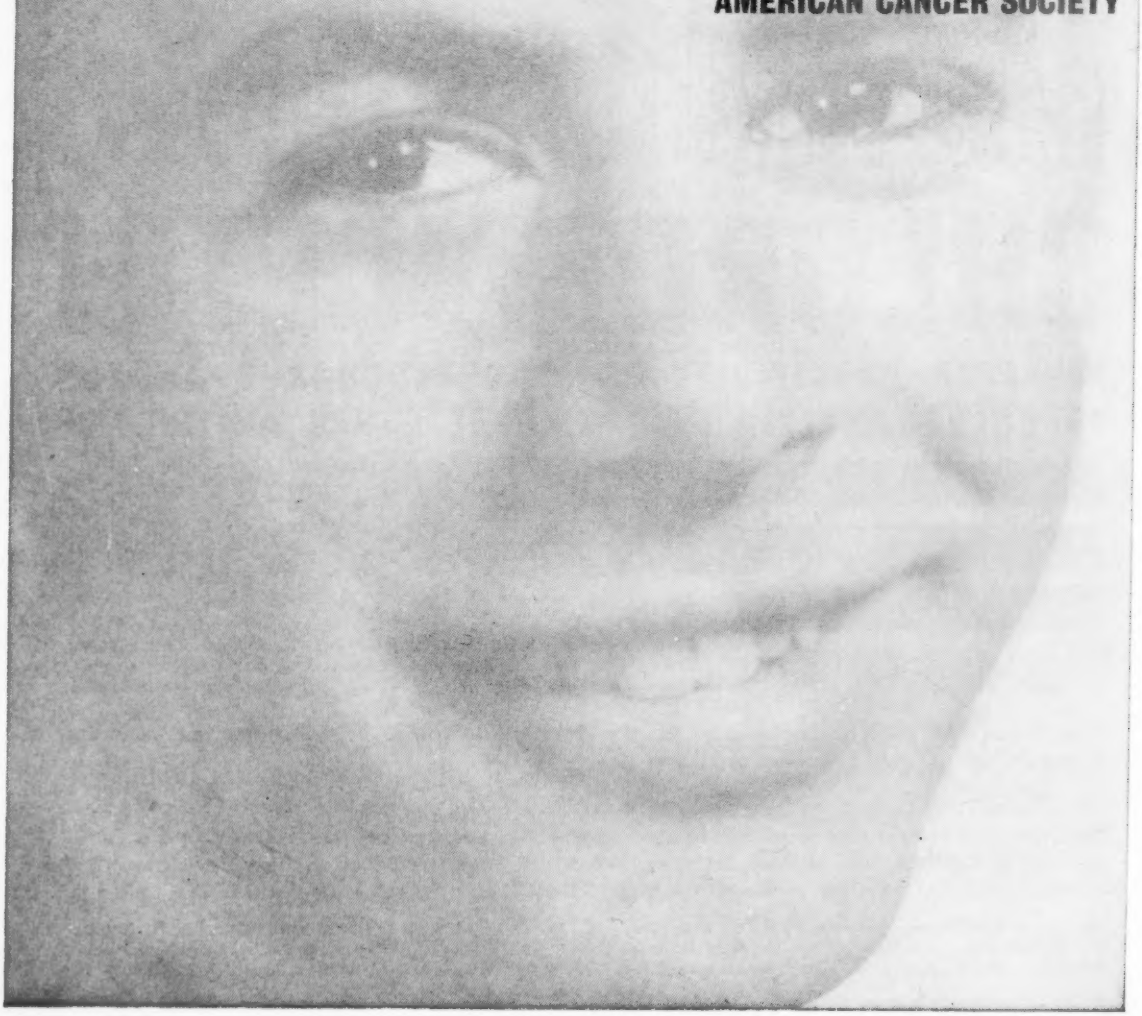
The effectiveness of this educational tool will depend on the support of the entire community—teachers, parents and, most of all, physicians. Many physicians are participating in the presentation of the filmstrip.

This is another example of how the medical profession and the American Cancer Society can cooperate in essential public education in the fight against cancer.

AMERICAN CANCER SOCIETY



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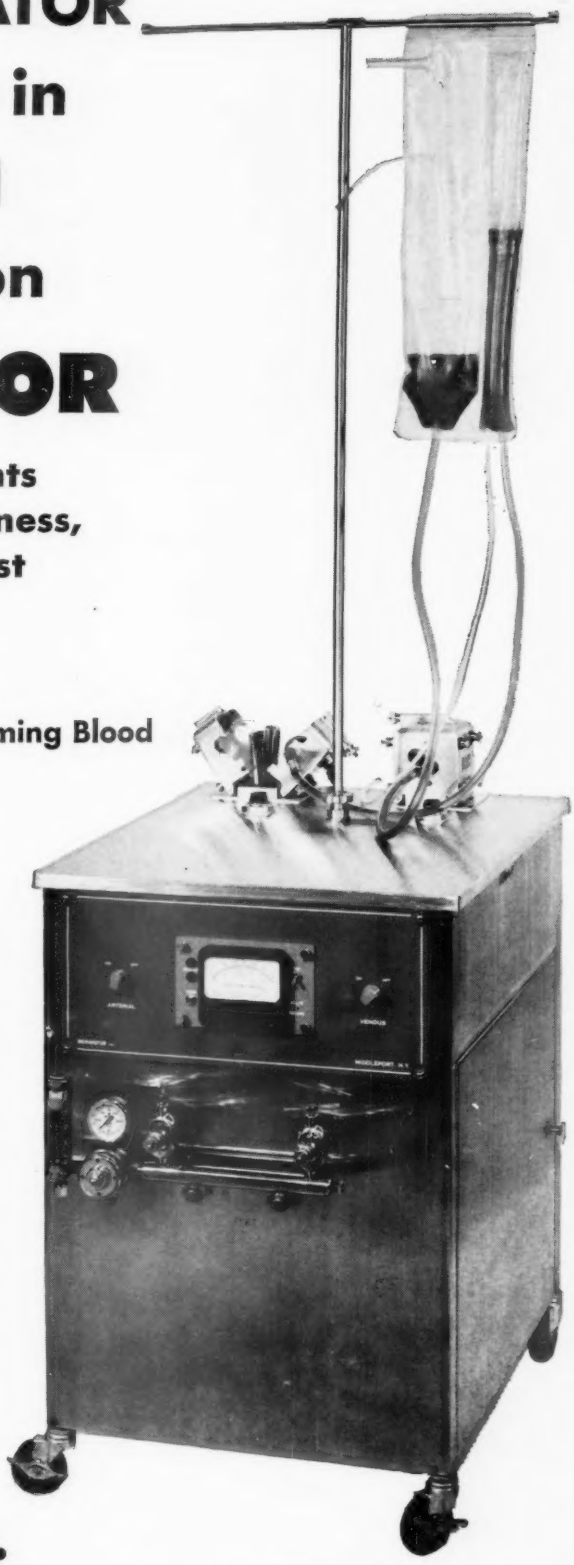

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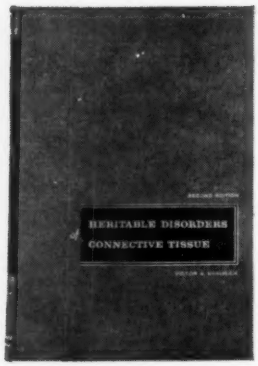

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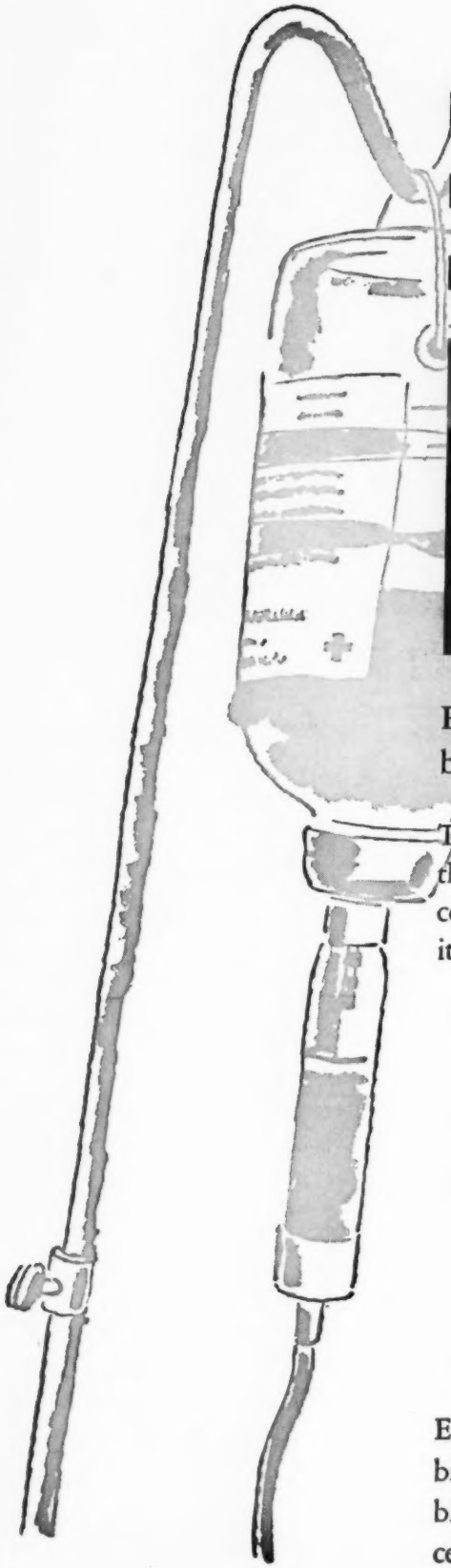

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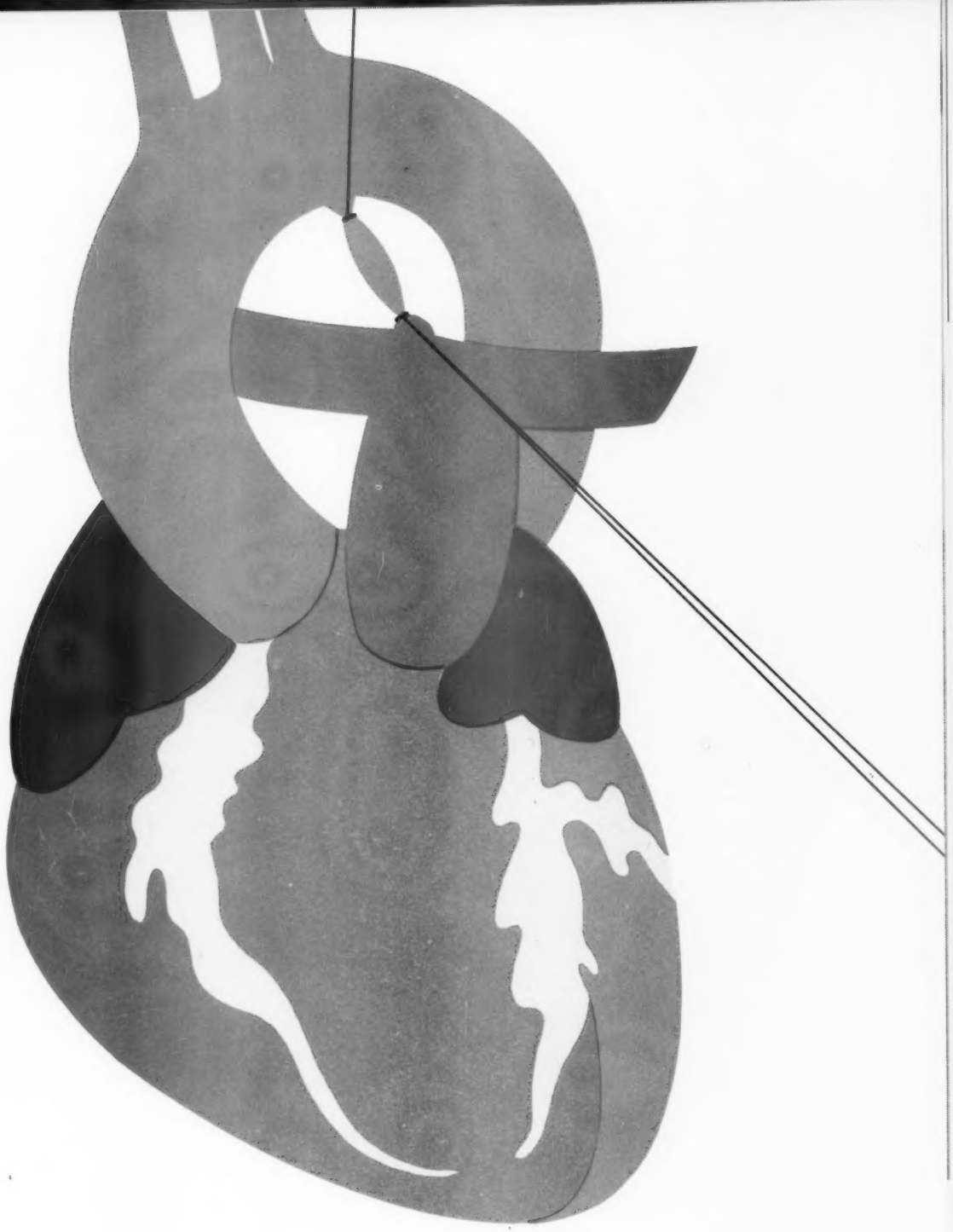

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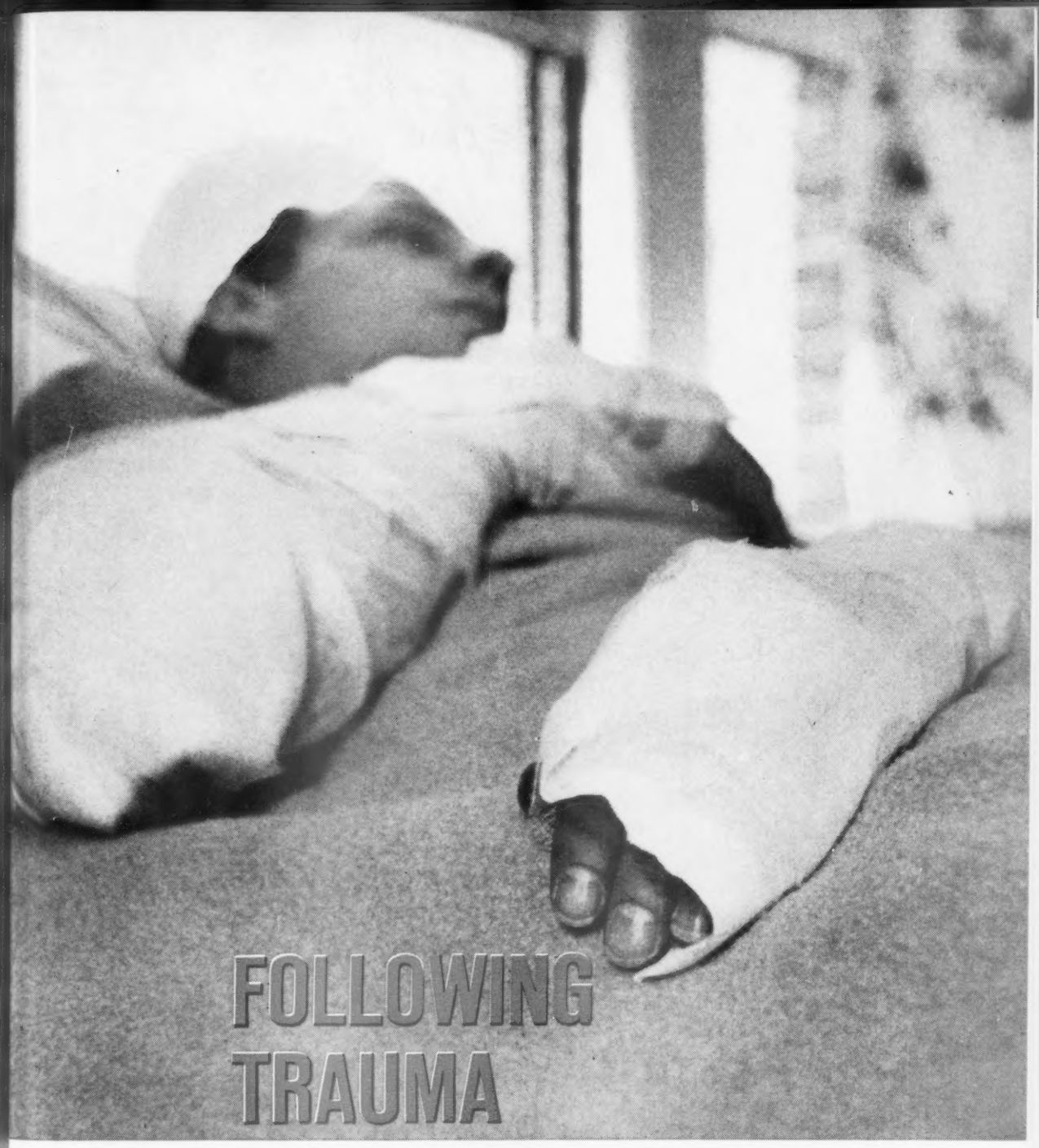

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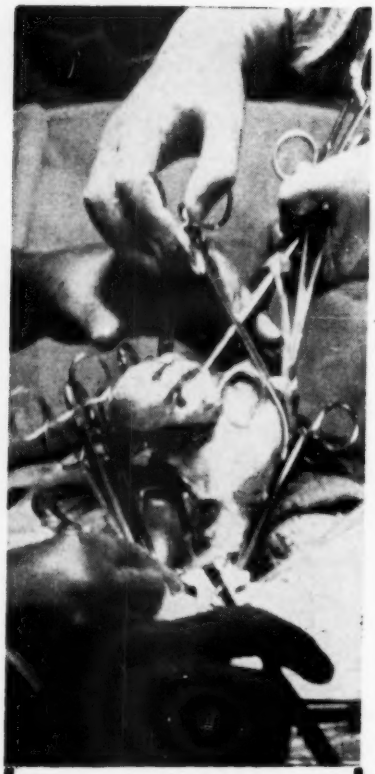

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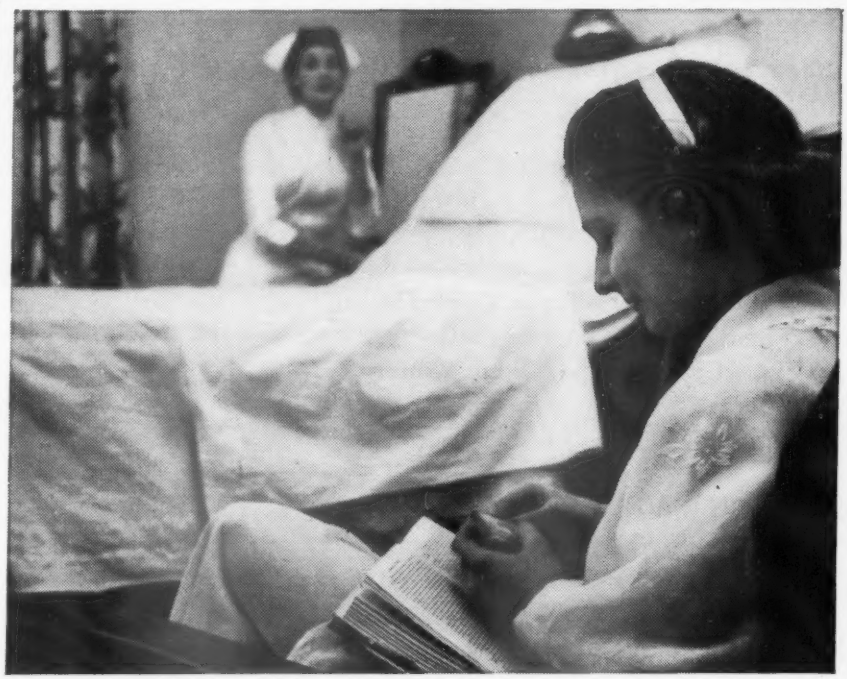

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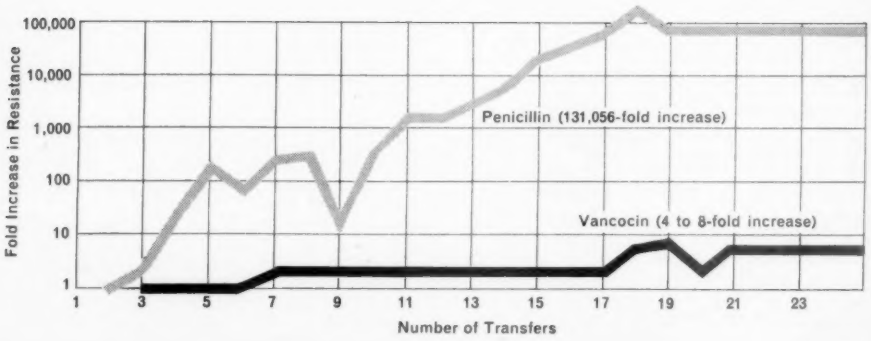

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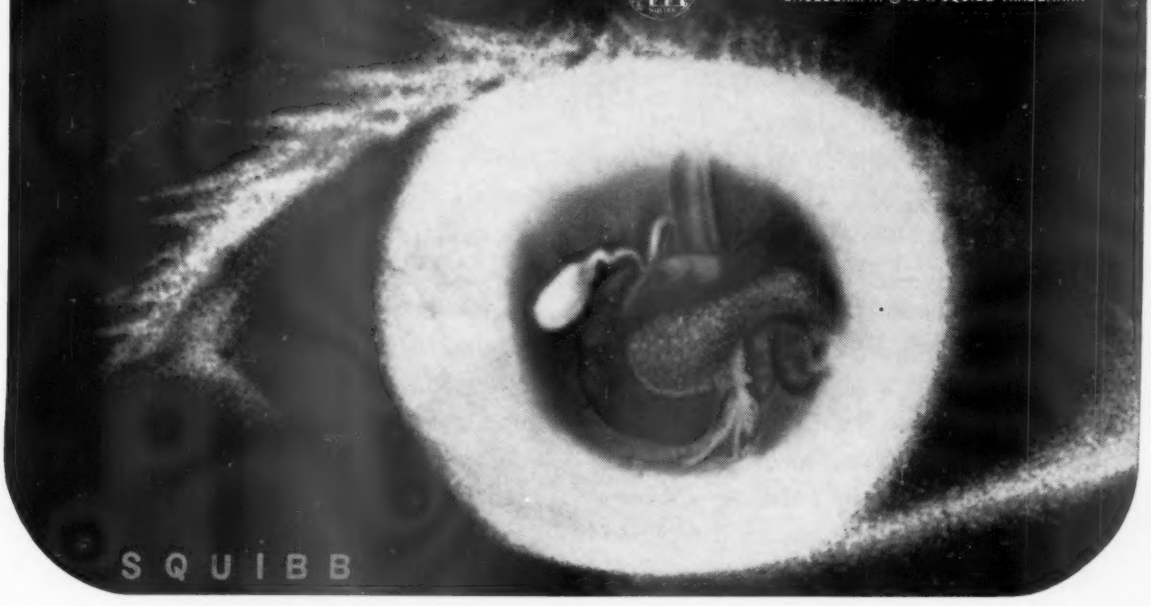

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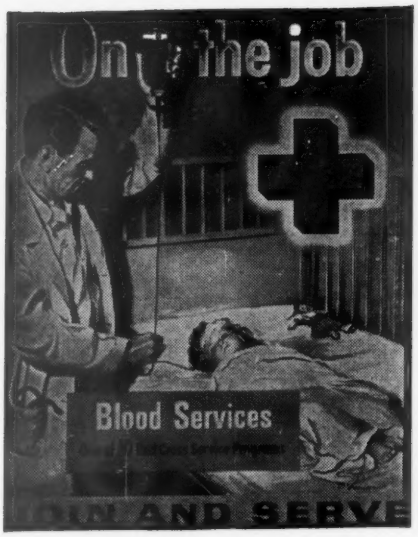

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